AAV2-hRPE65v2-101 SYNOPSIS

Name of Company: **Spark Therapeutics** 3737 Market Street, Suite 1300 Philadelphia, PA 19104 **Name of Finished Product:** voretigene neparvovec **Name of Active Ingredient(s):** AAV2-hRPE65v2	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	***(For National Authority Use Only)***

Title of Study: A Phase 1 Safety Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human *RPE65* into the Retinal Pigment Epithelium (RPE).

Number and Name of Study Center(s):

001: The Children's Hospital of Philadelphia, Department of Ophthalmology, 34th and Civic Center Blvd, Philadelphia PA 19104 [Administration site for all subjects]

002: Second University of Naples, Department of Ophthalmology, Via S Pansini 5, 80131 Naples Italy [Referral/follow-up site for 5 subjects from September 2007 through June 2011]

Study Period:	**Clinical Phase:**
First subject, first visit: 25 September 2007 Last subject, last visit: 14 October 2014 (data cut-off date for this report)	Phase 1

Objectives:

Primary: To determine the safety and tolerability of subretinal administration of AAV2-hRPE65v2 to subjects with LCA due to retinal pigment epithelium 65 kDa protein (RPE65) mutations.

Secondary: To assess the objective clinical measures of efficacy in human subjects.

Endpoints:

Safety Assessments

Safety assessments included physical examination with vital signs, adverse event (AE) recording, concomitant medications, clinical labs including serum chemistries and hematology, serum for adeno-associated virus (AAV) and RPE65-specific neutralizing antibodies and antigen-specific reactivities, peripheral blood and tear quantitative polymerase chain reaction (QPCR) to detect vector spread, serial ophthalmic exams (including visual

acuity measurement, slit lamp examination, applanation tonometry and gonioscopy as needed in cases of increased intraocular pressure), and direct and indirect ophthalmoscopy.

Efficacy Assessments

Efficacy assessments included visual/retinal function measured using visual acuity testing, visual field testing (Goldmann perimetry), and electroretinography (ERG) as key outcome measures. Other outcome measures of visual/retinal function included contrast sensitivity, color vision testing, pupil function testing, and mobility testing. Ocular motility measurements assessing fixation and quality of life assessments were also included.

Methodology:
This was a Phase 1 open label dose escalation safety study of gene transfer by subretinal administration of AAV2-hRPE65v2. Up to 12 subjects eight years of age or older at the time of vector administration were to be recruited, each to receive a single unilateral dose. Three dose cohorts were planned including 1.5E10, 4.8E10, and 1.5E11 vector genomes of AAV2-hRPE65v2.

Number of Subjects (planned and analyzed):
Planned**:** 12

Analyzed: 12

Diagnosis and Criteria for Inclusion:

Inclusion Criteria:

1. Willingness to adhere to protocol and companion protocol for long-term follow-up as evidenced by written informed consent or parental permission and subject assent.
2. Adults and children diagnosed with LCA.
3. Molecular diagnosis of LCA due to RPE65 mutations (homozygotes or compound heterozygotes) by a Clinical Laboratory Improvement Amendments of 1988 (CLIA)-certified laboratory.
4. Age eight years old or older at the time of administration.
5. Visual acuity ≤ 20/160 or visual field less than 20° in the eye to be injected.

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Exclusion Criteria

1. Unable or unwilling to meet requirements of the study.
2. Participation in a clinical study with an investigational drug in the past six months.
3. Pre-existing eye conditions that would preclude the planned surgery or interfere with the interpretation of study endpoints (for example, glaucoma, corneal or lenticular opacities).
4. Lack of sufficient viable retinal cells as determined by non-invasive means, such as optical coherence tomography (OCT) and/or ophthalmoscopy. Specifically, if indirect ophthalmoscopy reveals less than 1 disc area of retina which is not involved by complete retinal degeneration (indicated by geographic atrophy, thinning with tapetal sheen, or confluent intraretinal pigment migration), these eyes will be excluded. In addition, in eyes where OCT scans of sufficient quality can be obtained, areas of retina with thickness measurements less than 100 μm, or absence of neural retina, will not be targeted for delivery of AAV2-hRPE65v2.
5. Complicating systemic diseases or clinically significant abnormal baseline laboratory values. 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 central nervous system (CNS)/optic nerve involvement). Also excluded would be subjects with immuno-compromising diseases, as there could be susceptibility to opportunistic infection (such as CMV retinitis). 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). Subjects with juvenile rheumatoid arthritis could be excluded due to increased infection risk after surgery due to poor wound healing. Subjects who are positive for hepatitis B, C, and human immunodeficiency virus (HIV) will be excluded.
6. Prior ocular surgery within six months.
7. Known sensitivity to medications planned for use in the peri-operative period.
8. Individuals of childbearing potential who are pregnant or unwilling to use effective contraception for the duration of the study.
9. Any other condition that would not allow the potential subject to complete follow-up examinations during the course of the study and, in the opinion of the investigator, makes the potential subject unsuitable for the study.

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10. Subjects will be excluded if immunological studies show presence of neutralizing antibodies to AAV2 above 1:1000.

Test Product, Dose, Mode of Administration and Lot Number:
AAV2-hRPE65v2 was supplied in 1 mL aliquots in 1.5 mL cryovials as a suspension at a concentration of approximately 5E12 vector genomes (vg)/mL. A total volume of 150 or 300 microliters of AAV2-hRPE65v2 was injected into the subretinal space. The low (1.5E10 vg) and middle (4.8E10 vg) dose cohorts were administered in a volume of 150 microliters and the high dose (1.5E11 vg) was administered in a volume of 300 microliters. The AAV2-hRPE65v2 batch used was AAV2-hRPE65v2 Lot 142-07001 (DOM: 03-Jan-2007).

Duration of Treatment: This study involved a single subretinal injection of the test article with at least 1 year of post-injection follow-up.

Reference Therapy, Dose and Mode of Administration, Lot Number:

There was no placebo or comparative treatment group in this study.

Criteria for Evaluation:

Safety Assessments

Safety assessments included:

- Physical examination with vital signs.
- Adverse event recording.
- Concomitant medications.
- Clinical labs including serum chemistries and hematology, serum for AAV and RPE65-specific neutralizing antibodies and antigen-specific reactivities, peripheral blood and tear QPCR to detect vector spread.
- Serial ophthalmic exams (including visual acuity measurement, slit lamp examination, applanation tonometry and gonioscopy as needed in cases of increased intraocular pressure).
- Direct and indirect ophthalmoscopy.

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Efficacy Assessments

Efficacy assessments included:

- Visual and retinal function analysis using visual acuity testing, visual field testing (Goldmann perimetry), and ERG as key outcome measures. Other outcome measures of visual function included contrast sensitivity, color vision testing, pupil function testing, and mobility testing.
- Ocular motility measurements to assess improvements in fixation.
- Quality of life assessments.

Statistical Methods:

Descriptive statistics (mean, standard deviation, median, minimum, and maximum values) were tabulated for the study population. Subject disposition, demographic and baseline characteristics, extent of exposure and study termination/withdrawal information were presented, as well as safety, esoteric testing information, and efficacy information. Descriptive statistics (number and percentage by dose cohort for categorical data; mean, median, range, standard deviation and N for continuous data) were presented for each of the evaluable parameters for change from baseline as well as value at each time point. AE information was summarized by dose cohort and narratives were used in presentation of the data for safety monitoring. Serious adverse events (SAEs) were summarized similarly and narratives presented. Clinical laboratory values were summarized by time point, subject, and dose cohort. Values and changes from baseline at each time point were tabulated.

Summary and Conclusions:

Safety Results:

- Subretinal administration of AAV2-hRPE65v2 was generally well tolerated, both locally and systemically.
- No deaths or related serious adverse events were reported. One subject experienced a SAE of anal fistula. The SAE was mild in severity and considered unlikely to be related to study drug or study drug administration procedure. The event was recovered/resolved with no sequelae.
- No treatment-emergent AEs (TEAEs) were considered related to the study drug; 10 (83%) subjects experienced TEAEs considered related to the study drug administration

procedure. Most TEAEs were mild in severity and recovered or resolved with no sequelae.

- Persistence or recurrence of conjunctival hyperaemia was seen in eight (67%) subjects and classified as a TEAE. These events included findings of surface irritation (eye), suture reaction, suture irritation, and/or suture allergy, and were, in some cases, attributed to the use and persistence of slow-absorbing suture material at the incision site. Symptoms of foreign body sensation were managed with topical steroids and antibiotic drops as standard post-operative care for subretinal surgery.
- One subject developed an asymptomatic macular hole that was noted two weeks after surgery. This adverse event did not prevent improvement in retinal/visual function, including visual acuity. At the time of this report, the appearance of the macular hole in This subject has remained stable for more than six years; monitoring of the first injected eye continues under the follow-on Phase 1 study AAV2-hRPE65v2-102.
- No clinically significant changes in laboratory tests or physical examinations were observed at any time point; five (42%) subjects had isolated increases or decreases in blood pressure or heart rate, with no apparent safety signals associated with these events and no adverse events linked to changes in vital signs.

Efficacy Results:

- Visual acuity results indicated that seven of 12 (58%) subjects demonstrated a clinically significant LogMAR improvement of 0.3 or more, corresponding to an improvement of at least three lines (15 letters) on the eye chart, at Year 1. These improvements were sustained at the level of significance for the duration of follow-up for five of these seven subjects; the LogMAR improvement for two subjects was 0.24 and 0.25 at their last 101 study visit (Year 4 and Year 2, respectively), slightly below the accepted level of significance. At Year 1, 75% of subjects demonstrated improved visual acuity while at Year 2, 82% of subjects demonstrated improved visual acuity and at Year 3, 78% of subjects demonstrated improved visual acuity.
- Analysis of visual fields revealed a trend towards improvement in the injected eyes as compared to the uninjected eyes; however, given the difficulties in testing and the visit-to-visit variability, visual field is not considered a sensitive or reliable outcome measure for this patient population.
- Full-field light sensitivity threshold (FST) testing indicated that, in the majority of

evaluated subjects, the injected eye became more sensitive after AAV2-hRPE65v2 injection and remained so over the follow-up period. Overall, of the eight evaluable subjects for which sensitivity was measured both before and after injection, seven showed consistently increased light sensitivity in the injected eye while none of the subjects showed this increased light sensitivity in the uninjected eye.

- Pupillometry results indicated that the majority of subjects showed improved amplitudes of constriction after illumination with light in the experimental eye versus the control eye. This response was reflected by development of relative afferent pupillary defect whereby the injected eye showed a pupillary light reflex upon illumination with dim light after AAV2-hRPE65v2 injection whereas the contralateral (uninjected) eye showed no response with the same level of illumination.
- The improved ability of all of the children in the study to navigate under dim light conditions using their experimental eye after injection, but not their uninjected control eye, confirmed the importance of the results of light sensitivity measures (such as pupillometry and FST testing) with respect to day-to-day function.
- Overall, the results of this study indicate that the most consistent improvements after subretinal gene therapy with AAV2-hRPE65v2 were with respect to nyctalopia, or night blindness. The ability to navigate allows a subject more independence, decreases the danger they face as they carry out activities of daily living, and improves the quality of their lives.

CONCLUSIONS:

Subretinal injection of AAV2-hRPE65v2 was safe and well-tolerated in subjects ranging in age from eight to 44 years. The retinal and visual function changes observed following unilateral administration of AAV2-hRPE65v2 suggest durable improvements in subject vision. These improvements are in contrast to the progressive nature of inherited retinal degenerative conditions, in which subjects face a slow and inexorable deterioration of retinal and visual function that progresses until no useful vision remains.

Date of the Report: Final, 23 October 2015 (amended by CSR Amendment 002, EU, 08-Jun-2017)

Marketing Authorization Holder in the Rest of the World Countries
Novartis Pharmaceuticals

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Not applicable.

Publication(s)

1 MAGUIRE, A. M., HIGH, K. A., AURICCHIO, A., et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial. Lancet. 2009 Nov 7;374(9701):1597-605.[1]

2 MAGUIRE, A. M., SIMONELLI, F., PIERCE, E. A., et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. N Engl J Med. 2008 May 22;358(21):2240-8.

3 ASHTARI, M., CYCKOWSKI, L. L., MONROE, J. F., et al. The human visual cortex responds to gene therapy-mediated recovery of retinal function. J Clin Invest. 2011 Jun;121(6):2160-8.[2]

4 MELILLO, P., PECCHIA, L., TESTA, F. et al. Pupillometric analysis for assessment of gene therapy in Leber Congenital Amaurosis patients. Biomed Eng Online. 2012 Jul 19;11:40.

5 SIMONELLI, F., MAGUIRE, A. M., TESTA, F., et al. Gene therapy for leber's congenital amaurosis is safe and effective through 1.5 years after vector administration. Mol Ther. 2010 Mar; 18(3): 643–650.

6 TESTA, F., MAGUIRE, A. M., ROSSI, S., et al. Three-year follow-up after unilateral subretinal delivery of adeno-associated virus in patients with leber congenital amaurosis type 2. Ophthalmology. 2013 Jun;120(6):1283-91.

Investigators & Information on Study Centers

[1] Erratum in Lancet. 2010 Jan 2;375(9708):30.
[2] Erratum in J Clin Invest. 2011 Jul 1;121(7):2945.

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