AAV2-hRPE65v2-102 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 Follow-On Study to Evaluate the Safety of Re-Administration of Adeno-Associated Viral Vector Containing the Gene for Human *RPE65* [AAV2-hRPE65v2] to the Contralateral Eye in Subjects with Leber Congenital Amaurosis (LCA) Previously Enrolled in a Phase 1 Study.

Number and Name of Study Center(s):
01: The Children's Hospital of Philadelphia, Department of Ophthalmology, 34th and Civic Centre Blvd, Philadelphia, PA 19104

Study Period:	**Clinical Phase:**
First patient, first visit: 15-Nov-2010 Last patient, last visit: 10-Oct-2014 (data cut-off date for this report)	Phase 1

Objectives:
Primary: To assess the safety and tolerability of non-simultaneous, bilateral subretinal administration of AAV2-hRPE65v2.

Secondary: To evaluate the efficacy of contralateral eye administration of AAV2-hRPE65v2, using pre-injection measurements of the eye to be injected as a control.

Endpoints:
Safety Endpoints:
The primary objective was to evaluate the safety and tolerability of the study drug by recording all adverse events (AEs) and concomitant medications during the study. Safety assessments included physical exams including vital signs (blood pressure, pulse, temperature), pre- and post-administration serum chemistry including liver function panels [Serum glutamate oxaloacetic acid (SGOT)/Aspartate aminotransferase (AST), Serum glutamate pyruvic acid (SGPT)/Alanine aminotransferase (ALT), total Bilirubin] and renal function panels [Blood urea nitrogen (BUN), creatinine], hematology (red blood cell [RBC], hemoglobin, hematocrit, platelet count, white blood cell [WBC] with differential), and urinalysis; immunology studies for AAV antibodies (AAV Ab) and antibodies for retinal pigment epithelium 65 kDa protein (*RPE65* Ab); and peripheral blood mononuclear cells (PBMCs) using ELISPOT assay for cell-mediated immune response.

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Serial ophthalmic exams were also done including pupillary reaction, slit lamp examination, applanation tonometry, and gonioscopy, biomicroscopy and indirect ophthalmoscopy, fundus photography, and optical coherence tomography (OCT). Peripheral blood and tear polymerase chain reaction (PCR) were to be utilized to detect vector spread.

Efficacy Endpoints:
The secondary objective was to evaluate the efficacy of the study drug by assessing change in visual/retinal function through subjective, psychophysical and objective, physiologic tests. Measures to assess efficacy included mobility testing, pupillary light responses (PLR), full-field light sensitivity threshold (FST) testing, visual acuity testing, visual field testing (Goldmann perimetry), and contrast sensitivity.

Methodology:
The study was a Phase 1 follow-on study of gene transfer by subretinal re-administration of AAV2-hRPE65v2; eligible subjects were to receive an injection of 1.5E11 vg AAV2-hRPE65v2 in a total subretinal volume of 300 microliters (µL) to the previously uninjected, contralateral eye. Part 1 of the study involved three eligible subjects with a minimum 8-week interval between subjects for administration of AAV2-hRPE65v2. All subjects in Part 1 were to be evaluated through the Week 8 visit prior to proceeding to Part 2 of the study; Part 2 was to be contingent on Data and Safety Monitoring Board (DSMB) approval following review of this initial safety data from Part 1. Part 2 of the study was planned to involve up to nine eligible subjects remaining from the 12 initial Phase 1 study (Study 101) subjects.

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

Analyzed: 11 subjects

Diagnosis and Criteria for Inclusion:

Inclusion Criteria:

1. Prior participation in initial Phase 1 study (Study 101) with unilateral, subretinal administration of AAV2-hRPE65v2.
2. Visual acuity equal to or greater than light perception.
3. Sufficient viable retinal cells in the contralateral, previously uninjected eye, as determined by non-invasive means, such as OCT and/or ophthalmoscopy. Required to have either: *1)* an area of retina within the posterior pole of > 100 µm shown on OCT; *2)* ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the

posterior pole; or *3)* remaining visual field within 50° of fixation.

4. Willingness to adhere to protocol and long-term follow-up as evidenced by written informed consent or parental permission and subject assent (where applicable).

Exclusion Criteria:

Subjects were not to be excluded based on their gender, race or ethnicity.

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. 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.
4. Prior intraocular surgery within six months.
5. Known sensitivity to medications planned for use in the peri-operative period.
6. Pre-existing eye conditions, such as glaucoma, or complicating systemic diseases that would preclude the planned surgery or could 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 central nervous system [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 cytomegalovirus [CMV] retinitis).
7. Individuals of childbearing potential who are pregnant or unwilling to use effective contraception for four months following vector administration.
8. 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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Test Product, Dose, Mode of Administration and Lot Number:
All eligible subjects were planned to receive 1.5E11 vector genomes (vg) of AAV2-hRPE65v2 delivered to the subretinal space of the previously uninjected, contralateral eye. AAV2-hRPE65v2 was supplied in 1 mL aliquots in 1.5 mL cryovials as a suspension at a concentration of approximately 5E12 vg/mL. AAV2-hRPE65v2 was to be administered using a commercially available cannula that was designed for subretinal injection. 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 two years of post-injection follow-up.

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

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

Criteria for Evaluation:

Safety Assessments:
Safety assessments were to be done based on physical exams including vital signs (blood pressure, pulse, temperature), pre- and post-administration serum chemistry including liver function panels (SGOT/AST, SGPT/ALT, total Bilirubin) and renal function panels (BUN, creatinine), hematology (RBC, hemoglobin, hematocrit, platelet count, WBC with differential), and urinalysis. Blood collection was to include collection for standard tests described above as well as for immunology studies for AAV Ab and *RPE65* Ab. Peripheral blood mononuclear cells (PBMCs) were to be collected for research laboratory studies using ELISPOT assay; this is a sensitive and quantitative assay for cell-mediated immune response.

Serial ophthalmic exams including: pupillary reaction, slit lamp examination (to evaluate the anatomic state and inflammatory activity of the anterior segment), applanation tonometry, and gonioscopy (as needed in cases of increased intraocular pressure [IOP]) were to be performed. Biomicroscopy and indirect ophthalmoscopy, fundus photography, and OCT were also to be performed and changes in the ocular media were to be noted. Peripheral blood and tear PCR were to be utilized to detect vector spread. Adverse events and concomitant medications were to be recorded at all study visits. A pregnancy test was also to be performed on all female subjects either 11 years old or older or beyond the onset of menstruation, at a baseline visit prior to administration of AAV2-hRPE65v2 and on the day of surgery.

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Efficacy Assessments:

Efficacy endpoints were to assess change in visual/retinal function through subjective, psychophysical and objective, physiologic tests. Measures to assess efficacy included mobility testing, PLR, FST testing, visual acuity, visual field, and contrast sensitivity.

Visual acuity measures were to document any change in central vision, the ability to resolve images presented as shapes/letters of different size. Visual field parameters were to evaluate alterations in function of different regions of the retina.

Pupillometry was planned to objectively assess the improvement of the retinal function that was perceived by the brain as control of pupil constriction depends on a signal from the retina being relayed to the brain, and then back to iris sphincter muscles of the eye. Pupillary light responses (PLR) evaluation documented the time-course and degree of constriction of both pupils as a function of exposure of first one eye and then the other to light of different intensities. Mobility testing was to assess the improvements in the subject's ability to navigate a short obstacle course. Contrast sensitivity was to measure the subject's ability to discern targets presented at varying levels of contrast. Full field light sensitivity threshold testing was to evaluate the light sensitivity of the retina using first white light and then colored lights as stimuli.

Statistical Methods:

Descriptive statistics (mean, standard deviation, median, minimum, and maximum values) were to be tabulated for the study population. Subject disposition, demographic and baseline characteristics, extent of exposure and study termination/withdrawal information were to be presented, as well as safety, research 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 to be presented for each of the evaluable parameters for change from baseline as well as value at each time point. Adverse Event (AE) information was to be summarized by dose cohort and narratives were to be used in presentation of the data for safety monitoring. Serious AEs (SAEs) were to be summarized similarly and narratives presented. Clinical laboratory values were to be summarized by time point, subject, and dose cohort. Values and changes from baseline at each time point were to be tabulated.

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Summary and Conclusions:

<u>Safety Results</u>:

- All subjects received the protocol-specified dose of study drug.
- AAV2-hRPE65v2 was generally well tolerated by the subjects enrolled in the study. No deaths or discontinuations from the study due to AEs were reported.
- One SAE was reported in this study, a subject was reported with elevated IOP of Grade 4 in right eye resulting in hospitalization with a start date of 16-Apr-2012 (Day 151) and an end date of 19-Apr-2012 (Day 154). The SAE was moderate in severity and considered unlikely to be related to study drug. The SAE was deemed related to the use of a depo-steroid injection for a known rare complication of vitrectomy (endophthalmitis). The event was poorly controlled with IOP-lowering drugs and eventually required filtration surgery, which restored IOP to normal. During the period of poorly controlled elevated IOP, the subject suffered optic nerve damage (optic atrophy) that did not reverse.
- None of the subjects were reported with study drug related treatment-emergent adverse events (TEAEs), however, seven subjects were reported with administration procedure related TEAEs. Majority of the TEAEs were mild or moderate in severity.
- The most frequently reported TEAEs following administration of AAV2-hRPE65v2 by Medical Dictionary for Regulatory Activities (MedDRA) SOC were gastrointestinal disorders (n = 9; 81.8%) followed by eye disorders, infections and infestations; and renal and urinary disorders (n = 7; 63.6%). On the preferred term (PT) level the most frequently reported TEAEs were pyrexia, influenza, elevated blood creatinine, headache, hematuria and proteinuria (n = 4; 36.4%) followed by cataract, dellen, abdominal discomfort, nausea, vomiting and oropharyngeal pain (n = 3; 27.3%).
- There was no clear pattern of change in evaluated clinical laboratory parameters, though the relatively small sample size limits the interpretation of these data.
- For the overall study population, no marked changes in vital signs were observed at any study time point. There were no apparent effects of study treatment on the development or incidence of clinically significant abnormal vital signs findings.
- In fundus photography, no breaks or tears were evident. No inflammation was evident in

any subject except one (endophthalmitis in the Study 102-injected eye on Day 11, unlikely related to study drug, likely related to administration procedure).

- Optical coherence tomography (OCT) showed no breaks or tears and no inflammation in the Study 102-injected eye except for one subject. In this subject, a macular hole was reported in the Study 101-injected eye during the initial Phase 1 study (Study 101) and was ongoing with no change in the Phase 1 follow-on study (Study 102). Subretinal fluid and intraretinal fluid were absent in all the subjects enrolled in the study.
- With the exception of isolated subject visits for five of 11 subjects, IFN-γ ELISPOT for AAV capsid and *RPE65* were negative at the time points evaluated. In the majority of subjects enrolled in the study, minimal or no change in antibody titer to AAV capsid was measured at all time points following vector administration.
- No peripheral blood vector sequences were detected in six of 11 subjects at any time point. Similarly, no tear vector sequences were detected in four of 11 subjects at any time point. All peripheral blood and tear specimens were negative for vector sequences after Day 3, with the exception of one positive, non-quantitative serum specimen at Week 2.

Efficacy Results:

- The FST testing results confirmed consistently improved light sensitivity of the Study 102- injected eye in eight of 11 subjects; this increase was greater than the 10 dB cut-off considered significant in seven of 11 subjects. The change in light sensitivity (dB) from Baseline to Year 1 was greater for Study 102-injected eyes than for Study 101-injected eyes. This difference in change (reflecting improved retinal sensitivity) between Study 102-injected and Study 101-injected was 14.0636 and was statistically significant (P=0.0067).
- Mobility testing results showed improvements in functional vision at lower light levels in the same eight of 11 subjects. This indicated the potential to gain the capability to conduct additional activities of daily living over a wider range of ambient light levels, thus potentially improving the quality of life and independence.
- Without an uninjected contralateral or fellow eye as a control, pupillometry was of less utility than in the initial Phase 1 trial (Study 101) where the development of a relative afferent pupillary defect was observed in the majority of subjects.

- Visual acuity showed slightly improved vision in seven of 11 subjects in the Study 102-injected eye, but this did not reach the accepted level of clinical significance in any of the subjects using the Lange 2009 off-chart sensitivity analysis.
- Visual field testing showed large variability from visit to visit in all of the subjects, likely due to the difficulty in carrying out this test in subjects with very low vision, including difficulty of fixation caused by advanced macular disease and nystagmus.
- There was no trend in change of contrast sensitivity after contralateral eye injection of AAV2-hRPE65v2.

CONCLUSIONS:

Subretinal injection of AAV2-hRPE65v2 to the contralateral eye was safe and well-tolerated in subjects that had previously received a unilateral subretinal injection of AAV2-hRPE65v2. The retinal and visual function changes observed following this second administration of AAV2-hRPE65v2 suggest consistent, durable improvements in retinal sensitivity, as assessed by FST, and mobility testing through at least two years for eight of 11 subjects. The improvements reached the level of significance for seven of 11 subjects for FST (10 dB or more) and eight of 11 subjects from mobility testing (1 specified light level or more). These improvements are in contrast to 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.

Based on the results from both non-clinical and clinical studies, it is suggested that further dose escalation is not advisable. Therefore, the Sponsor decided to move forward with the Study 101 high dose/ Study 102 dose as optimal for Phase 3.

Date of the Report: Final, 23 October 2015 (as amended by CSR Amendment 001, EU, 09 June 2017)

Marketing Authorization Holder in the Rest of the World countries

Novartis Pharmaceuticals

Swiss Authorization date and authorization number

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Novartis Study Code

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EudraCT Number

Not applicable.

Publication(s)

1 BENNETT, J., WELLMAN, J., MARSHALL, K. A., et al. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial. Lancet. 2016 Aug 13;388(10045):661-72.

2 BENNETT, J., ASHTARI, M., WELLMAN, J., et al. AAV2 gene therapy readministration in three adults with congenital blindness. Sci Transl Med. 2012 Feb 8;4(120):120ra15.

Other Key Publications

3 CHUNG, D.C., MCCAGUE, S., YU, Z.F. et al. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. Clin Exp Ophthalmol. 2018 Apr;46(3):247-259.

4 CHUNG, D.C., BERTELSEN, M., LORENZ, B., et al. The Natural History of Inherited Retinal Dystrophy Due to Biallelic Mutations in the RPE65 Gene. Am J Ophthalmol. 2019 Mar;199:58-70.

5 ASHTARI, M., NIKONOVA, E. S., MARSHALL, K. A., et al. The Role of the Human Visual Cortex in Assessment of the Long-Term Durability of Retinal Gene Therapy in Follow-on RPE65 Clinical Trial Patients. Ophthalmology. 2017 Jun; 124(6): 873–883.

6 CHUNG, D. C., LEE, K., REAPE, K. Z., et al. Long-term Effect of Voretigene Neparvovec on the Full-Field Light Sensitivity Threshold Test of Patients with RPE65 Mutation-Associated Inherited Retinal Dystrophy – Post Hoc Analysis of Phase I trial data. Investigative Ophthalmology & Visual Science July 2019, Vol.60, 3398.

7 MAGUIRE, A., WELLMAN, J. & CHUNG DC. Year 4 results for a Phase 1 trial of voretigene neparvovec in biallelic RPE65-mediated inherited retinal disease. The American Society of Retina Specialists August 11-15 2017 Boston, MA.

8 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.

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