

Medical Officer's Consultative Review of BLA 125610
Ophthalmology

Submission date: May 16, 2017
Review date: December 18, 2017
Sponsor: Spark Therapeutics
Product: LUXTURN A, Voretigene neparvovec-rzyl (AAV2-hRPE65v2: adeno-associated viral vector serotype 2)
Pharmacologic Class: adeno-associated virus vector based gene therapy
Proposed Indication: For the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.

Background: AAV2-hRPE65v2 is an adeno-associated viral type 2 vector with a cytomegalovirus (CMV) enhancer and chicken beta actin (C β A) promoter driving expression of normal human retinal pigment epithelium 65 kDa protein (hRPE65) gene.

Clinical Trials:

ID	Investigators	Population	Design	Test Products	Reporting Period
AAV2-hRPE65v2-301 [Study 301]	Children's Hospital of Philadelphia (CHOP), Department of Ophthalmology 34 th and Civic Center Blvd Philadelphia, PA 19104 University of Iowa Hospitals and Clinics, Department of Ophthalmology and Visual Science, 200 Hawkins Dr, Iowa City, IA 52242	Adults and children, 3 years of age and older, with confirmed RPE65 mutations; visual acuity \leq 20/60 or visual field $<$ 20° for both eyes; sufficient viable retinal cells 21 \geq 16] Intervention Group & 10 \geq 8] Control Group (Study 301)	Two center, randomized, open label study	AAV2-hRPE65v2; 1.5x10 ¹¹ vg to each eye; sequential subretinal injections within 6 to 18 days (12 \pm 6 days)	Full CSR Report on all randomized intervention and control subjects through Year 1B and Year 1C, respectively [15-Nov-2012 to 16-Jul-2015]
Study 301 Addendum		20 Intervention Group & 9 Control Group (Study 301 Addendum 2016, also referred to as Study 301 / 302)			CSR Addendum Report on 20 intervention subjects that received AAV2-hRPE65v2 through at least Year 2B visits. Report on the first year of follow-up for the 9 control subjects who crossed over to treatment after at least 1 year of observation. [15-Nov-2012 to 18-May-2016]
AAV2-hRPE65v2-101 [Study 101]	CHOP Second University of Naples, Department of	Subjects 8 years of age and older with confirmed RPE65 mutations;	Open label, dose escalation	AAV2-hRPE65v2; 1.5x10 ¹⁰ vg, 4.8x10 ¹⁰ vg, or 1.5x10 ¹¹ vg;	Full CSR Report of 12 subjects who received single, unilateral injection of

	Ophthalmology, Isole 3, Edificio 15, Via Pansini, 5 80131 Napoli, Italy (follow-up site only, no administration of product)	visual acuity $\leq 20/160$ or visual field $< 20^\circ$ in the eye to be injected; sufficient viable retinal cells 12 [12]		subretinal; single, unilateral dose	AAV2-hRPE65-v2 through transfer to study 102 (after Year 1.5 to Year 4) or to Year 5 (for the one subject not eligible for study 102*) [25-Sep-2007 to 14-Oct-2014]
AAV2-hRPE65v2-102 [Study 102] and AAV2-hRPE65v2-102 [Study 102 Addendum 2015]	CHOP	Participation in Study 101; visual acuity equal to or greater than light perception; sufficient viable retinal cells in contralateral, previously uninjected eye 11 [12]	Follow-on study from Study 101	AAV2-hRPE65v2; 1.5x10 ¹¹ vg; subretinal; single, previously uninjected contralateral eye	Full CSR Report of 11 subjects (follow-on subjects from Study 101) who received single injection to contralateral eye through Year 2 (n=8) & 3 (n=3) visits; reflecting a total of 4 to 6 years of follow-up from initial (101 study eye) injection [15-Nov-2010 to 10-Oct-2014] CSR Addendum Report on 11 subjects (follow-on subjects from Study 101) who received single injection to contralateral eye through Year 3 (n=8) & 4 (n=3) visits; reflecting a total of 5 to 7 years of follow-up from initial injection [11-Oct-2014 to 08-Oct-2015]
Mobility Testing Validation Study [Study MTVS]	CHOP	Subjects 3 years of age and older who are normally sighted or visually impaired, with or without biallelic RPE65-mediated inherited retinal disease 54 [60]	Observational	None	Full Report Reporting on a study protocol designed to measure properties of the mobility test and to evaluate its construct validity, reliability, content validity, and ability to detect changes over time. [02-Nov-2011 to 05-Dec-2014]
Natural History of Individuals with Retinal Degeneration Due to Autosomal Recessive Mutations in the RPE65 Gene [Study NHx]	01: Belgium (Ghent) 02: Germany (Giessen) 03: USA (Boston, MA) 05: Denmark (Copenhagen) 06: USA (Portland, OR) 07: Brazil (Sao Paulo) 08: France (Montpellier)	Evaluable medical charts from subjects born between Jan-1963 and Dec-2010 with autosomal recessive mutation(s) in the RPE65 gene 70 ≥ 40	Retrospective medical chart review	None	Full Report Retrospective medical chart review and report on the natural history of retinal degenerative disease in individuals with autosomal recessive mutations in the RPE65 gene. [28-Jul-2014 to 05-Feb-2016]

Clinical Study #1

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) **Study Number:** AAV2-hRPE65v2-301

Study Design: Two center, 31 patients, open label, 2:1 randomized trial comparing voretigene neparvovec administered subretinally to its vehicle.

Ancillary Therapy: Subjects were to take an oral regimen of systemic corticosteroids beginning three days before the first administration of AAV2-hRPE65v2 (Day -3A). The initial dose was to be 1 mg/kg/day prednisone for seven days, with a maximum prescribed dose of 40 mg/day, regardless of the weight of the subject; this was to be followed by 0.5 mg/kg/day prednisone for an additional five days, with a maximum prescribed dose of 20 mg/day, regardless of the weight of the subject. The prednisone dose was to then be tapered further to 0.5 mg/kg/QOD (maximum 20 mg/QOD, regardless of weight) until three days prior to the second administration of AAV2-hRPE65v2 (Day -3B).

The prednisone regimen surrounding the second injection was to be the same as that surrounding the first injection, namely 1 mg/kg/day prednisone for seven days (maximum 40 mg/day, regardless of weight) followed by 0.5 mg/kg/day prednisone for an additional five days (maximum 20 mg/day, regardless of weight). This regimen was to begin three days prior to the second injection (Day -3B) and then continue through eight days after the second injection (Day 8B). Introduction of the prednisone regimen surrounding the second injection was to supersede the taper of the regimen surrounding the first injection. Subjects were to be on systemic corticosteroids for a minimum of 18 days up to a maximum of 30 days, depending on the timing of the second injection; Day 0B will occur twelve days (\pm 6 days) following Day 0A.

Surgical Procedure: Within 120 minutes prior to surgery, the eye was dilated. Topical anti-infective drops were also applied, followed at least five minutes later by topical nonsteroidal anti-inflammatory to minimize intraoperative miosis. Surgery was performed under general anesthesia supplemented by local (retrobulbar) anesthetic irrigation. The eye was prepped with 5% betadine solution placed in the conjunctival fornix and on the peri-ocular skin and draped under sterile conditions. The product injection apparatus was prepared on the sterile surgical field by attaching a Bausch and Lomb Storz® 39 gauge hydrodissection Retinal Cannula (REF E7365) to the male luer lock end of a 6 inch Eagle Laboratories Fluid Tubing Extension Kit (REF 169-30L-6) and connecting the female end to a 1 mL polycarbonate luer lock BD Syringe (REF 309628), which was loaded with the product by a pharmacist. The vector was injected through the tubing and the cannula to eliminate any air in the tubing and the volume of vector available for injection was confirmed.

A lid speculum was placed and a standard 3-port pars plana vitrectomy is performed, using 20-gauge instrumentation and visualization with an operating microscope. Conjunctival peritomy incisions were made with Westcott scissors for 120 degrees temporally, and 60 degrees superior nasally. Tenon's capsule was dissected from the underlying sclera. Episcleral hemostasis was achieved with bipolar cautery. A retrobulbar irrigation of 5 mL 0.5% bupivacaine hydrochloride [without epinephrine] was performed both to mechanically stabilize the globe and to provide postoperative analgesia.

Sclerotomy incisions were made 3.5 millimeters posterior to the corneoscleral limbus in the inferotemporal, superotemporal, and superonasal quadrants. A 7-0 vicryl suture was placed in a vertical

mattress configuration surrounding the inferotemporal sclerotomy and used to fixate the flange of the infusion cannula. The tip of the infusion cannula was directly visualized through the pupil to confirm its intravitreal position prior to initiating the infusion of balanced salt solution enriched with bicarbonate, dextrose, and glutathione. Infusion pressure was maintained at 30 mm Hg throughout the procedure, except during the subretinal injection.

Core vitrectomy was performed at high cutting rate (800-2500 cuts per minute) and low suction (80-150 mm Hg) settings. The vitreous was removed as completely as possible with special attention to remove any vitreous in the vicinity of the superior sclerotomy sites to avoid vitreoretinal traction induced by instruments passing into and out of the eye, and to prevent vitreous from occluding the tip of the 39-gauge subretinal injection cannula. After completion of the core vitrectomy, the posterior pole was explored for residual cortical vitreous using a silicone tipped 20-gauge cannula (Alcon/Grieshaber Microsurgical Instruments REF 8065 149520) with direct linear suction at 150 mm Hg. If posterior cortical vitreous was engaged, the hyaloid face was separated from the posterior pole with gentle sweeping motion of the cannula as suction was maintained. A complete posterior vitreous detachment (PVD) was confirmed when a glial ring is released from the optic nerve (Weiss ring) and/or there was no displacement of the silicone cannula by vitreous traction. At this point, the vitreous cortex is no longer attached to the macular area. The remaining vitreous was then removed as completely as possible with the vitreous cutting instrument, especially behind the sclerotomy incisions. The macular area was examined for the presence of an epiretinal membrane and if present, the membrane was mobilized with a membrane scraper (DORC- Tano brush, Backflush with brush needle 20G/0.9mm REF 1281.BD), and removed with intraocular forceps (Grieshaber Revolution DSPS 20 gauge ILM forceps REF 707.44).

Prior to subretinal injection of the test article, a volume between 0.1 and 0.5 mL of perfluorooctane liquid (Perfluoron® Liquid, Alcon Laboratories; Ontario, Canada REF 8065900164) was injected over the macula to cover the fovea. The infusion pressure was then reduced to 10 mm Hg in order to accommodate the additional intraocular volume added by the vector injection. The Storz® 39-gauge hydrodissection cannula was placed in the sclerotomy by the surgeon while the assistant handles the syringe containing the test article (AAV2-hRPE65v2 vector). The cannula tip was placed on the retina in the area of the papillomacular bundle, superotemporal to the optic nerve and superior to the macular center. The cannula was placed a minimum of 2 mm from the foveal center but posterior to the equator of the eye.

The injection is performed in two steps. First, the hydrodissection cannula was positioned so as to indent the retina and drape the retina over the tip. The surgeon directed the assistant to inject a small amount of the agent to confirm that the tip is not occluded and it was properly positioned. Next, if a bleb was raised, the test article was injected to deliver a total volume of 0.3 mL. If no bleb is created during the test injection, the cannula tip was repositioned and the sequence was repeated. Any AAV2-hRPE65v2 injected into the vitreous will be removed by gentle aspiration with the vitreous cutter. At the completion of the injection, the hydrodissection cannula was removed and the infusion pressure was restored to 30 mmHg.

Following subretinal injection of the vector, the retina was inspected with indirect ophthalmoscopy and scleral indentation. Any retinal breaks identified were treated with retinopexy prior to fluid-air exchange. If bleeding was seen at the injection site, intraocular pressure was raised with closed sclerotomy sites until hemostasis was achieved. Fluid-air exchange was performed with a silicone tipped backflow cannula (REF 1281.AD, Dutch Ophthalmic Research Company), carefully avoiding draining through the retinotomy created for the subretinal injection. Perfluoron® Liquid is removed at this time.

The sclerotomy sites were closed. A retrobulbar infusion of 1 mL triamcinolone acetonide solution (40 mg/mL) was delivered followed by conjunctival closure. Subconjunctival injection of 0.5 mL of 4 mg/mL steroid solution and 0.5 mL of anti-infective solution was administered. The ocular surface is dressed with one inch of a steroid/anti-infective ointment and a patch and eye shield was put in position and secured over the eye which received the test article.

Supine head positioning is instituted in the post-operative period to orient the eye such that the desired macular area of retina-RPE cell treatment was placed in the most dependent position. The subject was maintained in a supine position (or that required for positioning of the air bubble) except for meals and bathroom activity. Position was maintained for 24 hours or until resorption of the subretinal injection was complete.

Investigators:

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Patient Population:

1. Diagnosis of LCA due to RPE65 mutations; molecular diagnosis is to be performed, or confirmed, by a CLIA-certified laboratory.
2. Age three years old or older.
3. Visual acuity worse than 20/60 (both eyes) and/or visual field less than 20° in any meridian as measured by III4e isopter or equivalent (both eyes).
4. Sufficient viable retinal cells as determined by non-invasive means, such as OCT and/or ophthalmoscopy. Must have had either:
 - a. an area of retina within the posterior pole of > 100 µm thickness shown on OCT;
 - b. ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or
remaining visual field within 30° of fixation as measured by III4e isopter or equivalent.
5. Able to be evaluated on mobility testing. Evaluable was defined as:
 - a. 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.
 - b. 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 were to be excluded.

Patients were excluded if they:

1. Were unable or unwilling to meet requirements of the study.
2. Had prior participation in a study in which a gene therapy vector was administered.
3. Had participated in a clinical study with an investigational drug in the past six months.
4. Used 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.
5. Had prior intraocular surgery within six months.
6. Were known to be sensitive to medications planned for use in the peri-operative period.
7. Pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study.
8. Were pregnant or unwilling to use effective contraception for four months following vector administration.
9. Had in the opinion of the investigator, a condition that made the potential subject unsuitable for the study.

Group Assignment/Randomization:

Randomization was determined by order of enrollment, verification of study eligibility, and the participant's randomization stratum (see Section 9.1.1). Subjects were randomized in a 2:1 ratio to the Intervention or Control group, stratified by Screening age (≥ 10 years or < 10 years) and mobility testing category (≥ 125 lux or < 125 lux). Within each stratum, randomized blocks (block size of 3) governed the allocation to treatment group.

Reviewer's Comment: *Acceptable.*

Schedule of Assessments

Assessment	Screening Visit	Baseline Visit	Day -3A ¹	Day								Year 1B/C
				0A/B	1A/B	3A/B	8B ¹	14B	30B/C	90B/C	180B/C	
Vision and medical history, prior medications	X											
Physical Exam		X										X
Pregnancy test (if applicable)	X			X								
Begin prednisone			X									
Discontinue prednisone							X					
Vital signs		X		X	X	X		X				X
Hematology		X		X	X	X		X	X	X		X
Chemistry		X		X	X	X		X	X	X		X
Urinalysis		X		X	X	X		X	X	X		X
Virology	X											
PBMC collection		X							X	X		X
AAV Ab		X							X	X		X
Peripheral blood/tear PCR		X		X	X	X		X	X	X	X ²	X
Ophthalmic exam	X ³	X ³			X	X		X	X ³	X ³	X ³	X ³
Mobility testing	X	X							X	X	X	X
Pupillometry		X							X	X	X	X
Visual acuity tests	X	X			X ⁴	X ⁴		X ⁴	X	X	X	X
Visual field tests	X	X							X	X	X	X
Orientation and mobility assessment		X										X
Visual function questionnaire		X							X	X	X	X
Full-field light sensitivity threshold testing		X							X	X	X	X
Contrast sensitivity		X							X	X	X	X
AE recording		X		X	X	X		X	X	X	X	X
Concomitant medication recording		X		X	X	X		X	X	X	X	X

1 Days -3A and 8B were not study visits. Subjects were to begin taking systemic corticosteroids prescribed following confirmation of eligibility and randomization or crossover to the Intervention group.

2 Tear collection only.

3 Ophthalmic exams at these visits were to include OCT and fundus photography.

4 Ophthalmic exams at these visits were to include visual acuity testing to monitor recovery from surgery.

Window of Acceptable Timeframe for Subject Evaluations

Time point	≤ 90 days	± 2 days	± 5 days	± 30 days	± 60 days
Screening	Of Baseline				
Baseline	Of Day 0A				
Day 14B		X			
Day 30B/C			X		
Days 90B/C and 180B/C				X	
Year 1B/C				X	
Year 2B to Year 15B					X

Endpoints:

Mobility Testing (Primary Efficacy Endpoint)

The mobility testing change score was an ordinal measure of outcome. For each light and eye patching combination (resulting in at least six different tests at each time point), an individual may succeed or fail the mobility test. A subject's ability to navigate under defined light conditions may have improved, remained stable, or worsened.

The mobility testing change score was calculated using the Baseline estimated lower light sensitivity cut-off for each eye patching and light combination and at follow-up (Year 1B or 1C for the primary endpoint), the lowest achieved light level at which a subject passed. For calculation of the mobility testing change score, each lux level in the study was associated with a numerical code, as follows:

Lux	1	4	10	50	125	250	400	> 400
Score code	6	5	4	3	2	1	0	-1

Reviewer's Comment: *The applicant and the Agency were not in agreement with the primary endpoint. The Agency requested that the primary endpoint utilize the first treated eye. The applicant chose to use the bilateral response. While both are important measures, the bilateral response is potentially problematic because it reflects the better seeing eye, not necessarily the treated eye. While it would have been better to have equally proportional spacing between light levels, the scale is acceptable for establishing efficacy. Effectively, this test becomes a low light level acuity test.*

The secondary endpoints of the study were to compare the following between the two treatment arms:

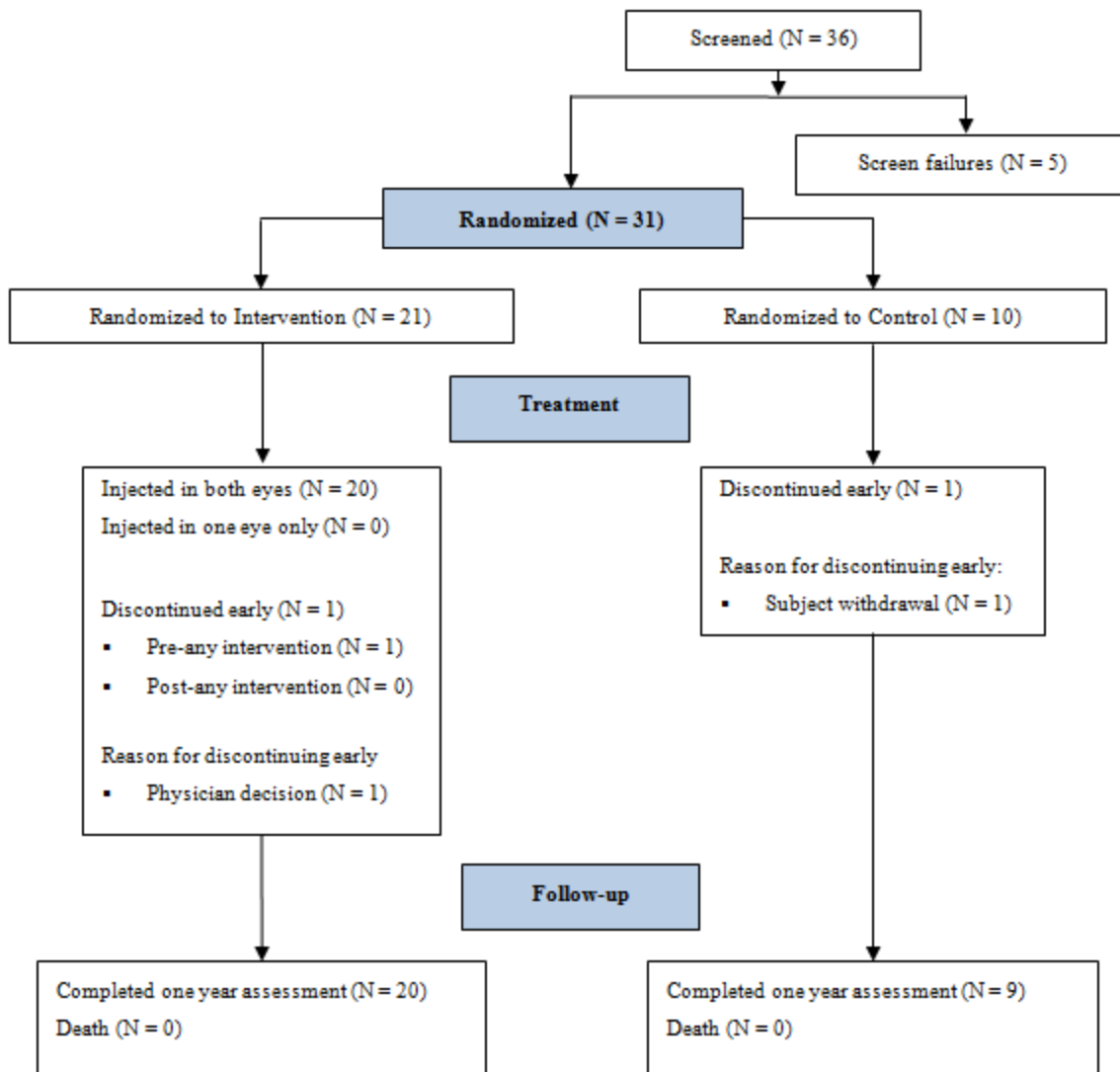
Full-field light sensitivity threshold testing: Average light sensitivity (averaged over both eyes) for white light at Year 1B/C as compared to Baseline

Full-field light sensitivity testing measures the light sensitivity of the entire visual field by recording the luminance at which a subject reports seeing the dimmest flash. The test is carried out on subjects with dilated eyes in a dark-adapted state (following a 40-minute dark adaption); subjects are seated in front of a Ganzfeld dome in which the light flashes are generated. The light sensitivity of each eye is measured separately by patching one eye (and then the other). A sound is generated at the time of the light flash, and at other times throughout the testing protocol, and the subject presses one button when they see a flash or a second button if they do not see a flash. Flashes of varying luminance (in a range spanning ~80 dB) are presented in a randomized order except that the series starts with dim flashes. From this data, an algorithm calculates the minimum luminance (for each eye) at which the subject reliably perceives light. Results of white light testing were used for the secondary analysis, though chromatic (red and blue) light testing was also performed.

Visual acuity: Average change in visual acuity at Year 1B/C as compared to Baseline

The ability to resolve standard optotype images presented as optotypes/letters corresponding to different visual angles, i.e., image size. This testing was to include age adapted tests, such as ETDRS testing or HOTV testing (which uses the letters H, O, T, V, which can be identified even by young children and all four of which center around a vertical axis). The level of central visual resolution is converted to a visual angle score (LogMAR) for comparison purposes. Subjects may have needed to undergo repeated testing sessions on different days to establish consistent Baseline measurements on psychophysical tests, such as visual acuity.

Subject Disposition/Enrollment



Screen Failures

Two subjects were not eligible based on mobility test performance

Subject (b) (6) (12-year-old) passed at 1 lux

Subject (b) (6) (50-year-old) had an accuracy score of >1 at 400 lux during Screening;

Subject (b) (6) (4-year-old) was not eligible based on attentional limitations;

Subject (b) (6) (12-year-old) was not eligible based on Screening visual acuity and visual field testing, specifically one eye did not meet (i.e., was better than) eligibility cut-offs for each test;

Subject (b) (6) (10-year-old) was not eligible based on lack of voluntary assent.

Two additional subject numbers were assigned; however, these individuals did not consent to participate in the study.

Subject (b) (6) decided not to participate prior to consent, and did not travel to University of Iowa to meet with the study team.

Subject (b) (6) disclosed HIV positive status to the University of Iowa study team prior to providing consent.

Numbering began with sixteen (16) to avoid duplication of subject numbers used in the Phase 1 studies.

Reviewer's Comment: *Acceptable.*

	Intervention (N = 21)	Control (N = 10)
Randomized	21	10
Injected in both eyes	20	
Discontinued early	1	1
Reason for discontinuing early	Physician decision	Withdrawal by subject
Protocol Deviations		
Assessment not done within required timeframe	5	2
Medication-related deviation ^a	5	1
A required assessment was not done	4	0
Inclusion criteria ^b	1	0
Site		
Children's Hospital of Philadelphia, United States	11 (52%)	8 (80%)
University of Iowa, United States	10 (48%)	2 (20%)
Strata: Age (at Screening)		
Age < 10 years	9 (43%)	4 (40%)
Age ≥ 10 years	12 (57%)	6 (60%)
Strata: Mobility testing level (at Screening)^a		
Pass at < 125 lux	12 (57%)	4 (40%)
Pass at ≥ 125 lux	9 (43%)	6 (60%)

^a For subjects in the Intervention group, all medication-related deviations were associated with alterations in prednisone/prednisolone dosing regimen.

^b Subject (b) (6) was deemed ineligible post-surgery upon discovery of passing at 1 lux with both eyes at Screening (i.e., violation of inclusion criterion #6b).

Reviewer's Comment: *It is unclear why there were four times as many control subjects seen at CHOP compared to Iowa, although the stratification factors are likely to have contributed to the distribution.*

The four occurrences of “a required assessment was not done” included one occurrence of fundus photography not completed due to camera malfunction ((b) (6) [Day 30B]), two occurrences of individual lab tests not done ((b) (6) [Day 0A] and ((b) (6) [Day 3A]), one occurrence of urine specimen not obtained ((b) (6) [Day 0A]). All protocol deviations are described by subject in Listing 16.2.2.3, selected protocol deviations are described below in additional detail.

Subject ((b) (6)): The Year 1 Mobility Testing (MT) was repeated at an unscheduled visit; both visits were recorded in the CRF database. As described in Section 11.4.2.2.1, an additional sensitivity analysis, using the MT Year 1 repeat visit data only, was performed for this subject. This subject’s Baseline MT testing occurred prior to 8-Apr-2013, by which time discrepancies in the pre-set luminance levels at the Iowa site were corrected; however, this subject performed Baseline MT at luminance levels of ≥ 50 lux, which were less affected. Though measurement of the light levels was not performed on the day of Baseline testing for this subject, it is believed (based on light meter readings approximately 10 days later and prior to any adjustments) that 250 lux was within specification (within 20% across five measured locations on the course) and that 125 lux was just outside of this specification (namely a reading within 21% for one of these five locations). Specified levels of 1, 4, 10 and 50 lux were all believed to be out of specification, namely more than 20% higher than they should have been; however, the subject nonetheless failed at “50 lux” at Baseline, establishing a sub-sensitivity cut-off light level for this visit. Also for this subject, FST data was missing at Baseline, Day 30B, Day 90B, and Day 180B, as the minimal required testing was considered unreliable for these visits.

Subject ((b) (6)): At Baseline, the sub-sensitivity cut-off light level for the bilateral testing condition was not determined during MT. As described in Section 11.2.2.5, conventions from the SAP were consistent with the subject’s Screening MT performance.

Subject ((b) (6)): A violation of inclusion criterion #6b occurred in that the subject was determined to have passed Screening mobility test runs at 1 lux. This violation was discovered on 10-Feb-2014, after the subject received bilateral vector administrations (October 2013) at the University of Iowa site. Also for this subject, the Baseline subsensitivity cut-off light level was not determined for the bilateral testing condition. As described in Section 11.2.2.5 and Section 11.4.2.2.1, an additional sensitivity analysis, in which the Screening MT performance was carried forward, was performed for this subject.

Subject ((b) (6)): The Year 1B MT was repeated due to a loss of video recordings.

Subject ((b) (6)): The Baseline MT was repeated due to inadvertent change in light levels, from a language interpreter leaning on the lighting panel and increasing luminance thereby negating dark adaption, during the first testing.

Subject ((b) (6)): The Baseline MT was repeated outside of the 90-day protocol window; subsensitivity light level may have not been determined at Baseline.

Subject ((b) (6)): The Baseline MT was repeated outside of the 90-day protocol window; subsensitivity light level may have not been determined at Baseline.

Demographics

Parameter/Category/Statistic	Children's Hospital of Philadelphia (N = 19)		University of Iowa (N = 12)	
	Intervention (N = 11)	Control (N = 8)	Intervention (N = 10)	Control (N = 2)
Age at Randomization (years)				
N	11	8	10	2
Mean (SD)	12.6 (8.4)	12.5 (6.9)	17.0 (14.7)	29.5 (2.1)
Range (min, max)	5, 33	4, 24	4, 44	28, 31
Quartiles (25th, median, 75th)	6, 11, 18	8, 10, 19	5, 11, 34	28, 30, 31
Male, n (%)	6 (55%)	3 (38%)	3 (30%)	1 (50%)
Race, n (%)				
White	8 (73%)	6 (75%)	6 (60%)	1 (50%)
Asian	3 (27%)	2 (25%)	0	0
American Indian or Alaska Native	0	0	2 (20%)	1 (50%)
Black or African American	0	0	2 (20%)	0
Ethnicity, n (%)				
Not Hispanic or Latino	8 (73%)	8 (100%)	8 (80%)	1 (50%)
Hispanic or Latino	3 (27%)	0	2 (20%)	1 (50%)
Country, n (%)				
United States	7 (64%)	4 (50%)	10 (100%)	2 (100%)
Netherlands	1 (9%)	2 (25%)	0	0
Belgium	0	1 (13%)	0	0
Canada	1 (9%)	0	0	0
India	1 (9%)	0	0	0
Italy	0	1 (13%)	0	0
Mexico	1 (9%)	0	0	0

Distribution of Lowest Light Levels Passed Unilaterally at Baseline (ITT)

	Intervention (N = 21)		Control (N = 10)	
Lux level, n (%)	First Eye	Second Eye	First Eye	Second Eye
1	0	0	0	0
4	0	0	1 (10%)	1 (10%)
10	4 (19%)	7 (33%)	0	2 (20%)
50	10 (48%)	8 (38%)	4 (40%)	1 (10%)
125	2 (10%)	2 (10%)	4 (40%)	4 (40%)
250	1 (5%)	1 (5%)	0	1 (10%)
400	0	1 (5%)	0	0
>400	4 (19%)	2 (10%)	1 (10%)	1 (10%)

Source data: [Table 14.1.1.13](#) and [Listing 16.2.6.1.3](#).

Distribution of Lowest Light Levels Passed Bilaterally at Baseline (ITT)

Lux level, n (%)	Intervention N = 21	Control N = 10
1	0	0
4	4 (19%)	1 (10%)
10	5 (24%)	2 (20%)
50	7 (33%)	5 (50%)
125	3 (14%)	1 (10%)
250	0	0
400	0	0
> 400 ^a	2 (10%)	1 (10%)

Two subjects from the Iowa site ((b) (6) and (b) (6)) were missing the sub-sensitivity cut-off light level for the bilateral testing condition at Baseline. In the case of Subject (b) (6) (Control), conventions from the SAP, which assume the lowest level tested reflects the estimated lower light sensitivity cut-off level, were consistent with Screening MT performance; however, in the case of Subject (b) (6) (randomized to Intervention and subsequently determined to be an eligibility violation), an alternate analysis carrying Screening MT performance forward is described in Section 11.4.2.2.1.

Efficacy Results

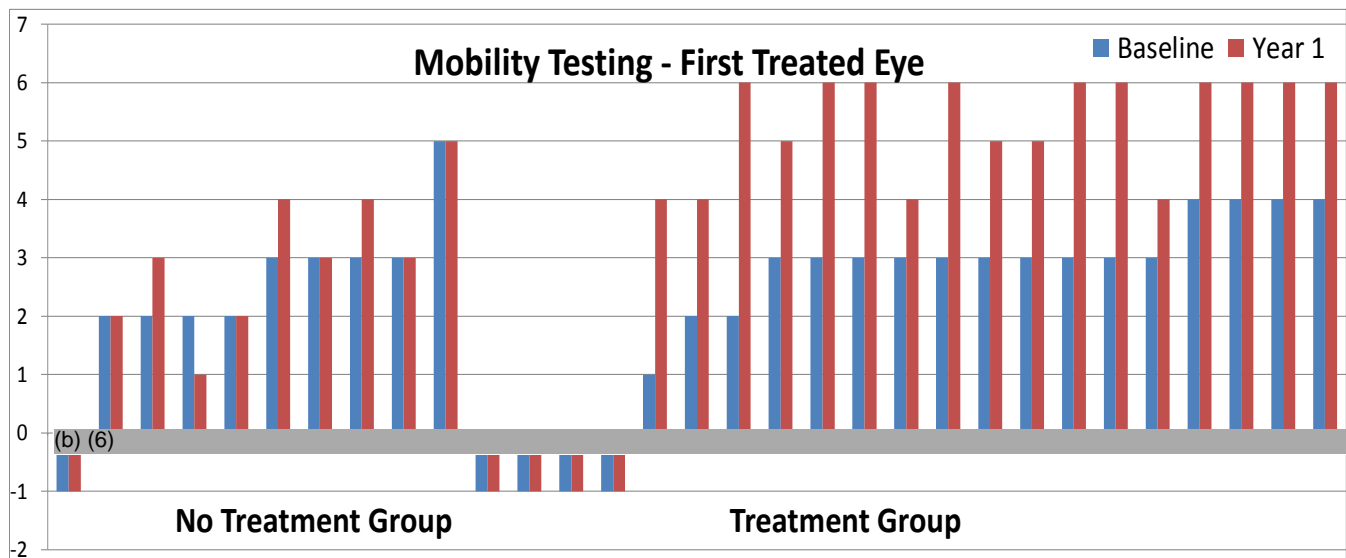
Mobility Testing

MT change score: first assigned eye, Year 1 compared to baseline (ITT) ITT population (N=31)

First eye	Intervention N=21	Control N=10	Difference (95% CI) (Intervention- Control)	Observed p-value	Permutation test p-value
Change score	1.9 (1.2)	0.2 (0.6)	1.7 (0.89, 2.52)	< 0.001	0.001
Mean (SD)					
Range (min, max)	0, 4	-1, 1			
Quartiles (25th, median, 75th)	1, 2, 3	0, 0, 1			

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.

E:\proj\Spark 301\programs\t_luxscore.sas v.004 (last run: 07/25/2016, 16:22) t_luxscore1st.rtf

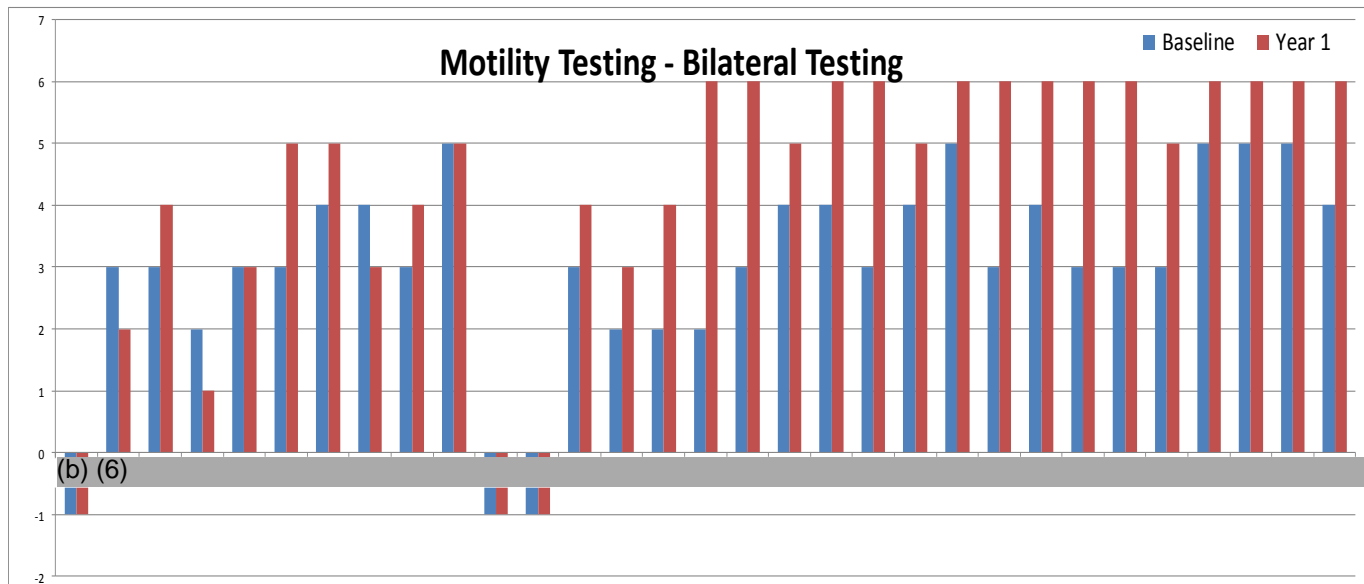


Reviewer's Comment: Subjects starting with a score of -1 did not improve with or without treatment. I consider a two- step improvement to be clinically significant. A one-step improvement is within the variation observed with testing. No subject in the no-treatment group improved by 2 steps. In the treatment group 15 out of 21 improved by two steps.

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

MT Change Score	Intervention (N = 21)	Control (N = 10)	Difference (95% CI) (Intervention- Control)	Observed <i>p</i> -value	Permutation Test <i>p</i> -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. Data Source: [Table 14.2.2.1](#), [Listing 16.2.6.1.1](#) through [Listing 16.2.6.1.4](#).



Reviewer's Comment: Subjects starting with a score of -1 did not improve with or without treatment. I consider a two- step improvement to be clinically significant. A one-step improvement is within the variation observed with testing. No subject in the no-treatment group improved by 2 steps. In the treatment group 15 out of 21 improved by two steps.

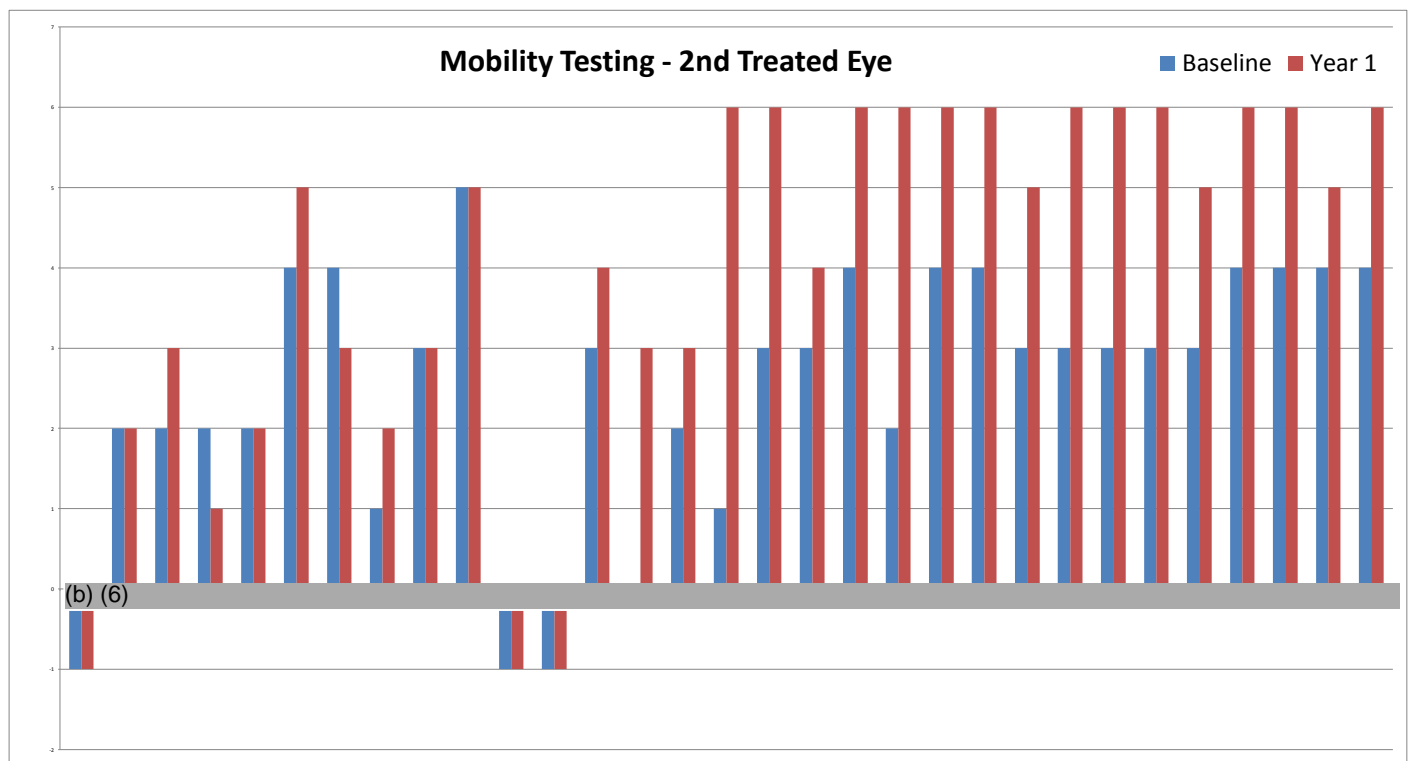
**MT change score: second assigned eye, Year 1 compared to baseline
(ITT) ITT population (N=31)**

<i>Second eye</i>	<i>Intervention N=21</i>	<i>Control N=10</i>	<i>Difference (95% CI) (Intervention- Control)</i>	<i>Observed p-value</i>	<i>Permutation test p-value</i>
Change score					
Mean (SD)	2.1 (1.2)	0.1 (0.7)	2.0 (1.14, 2.85)	< 0.001	< 0.001
Range (min, max)	0, 5	-1, 1			
Quartiles (25th, median, 75th)	1, 2, 3	0, 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.

Database lock: 2015-08-24

E:\proj\Spark 301\programs\t_luxscore.sas v.004 (last run: 07/25/2016, 16:22) t_luxscore2nd rtf



Reviewer's Comment: *Subjects starting with a score of -1 did not improve with or without treatment. I consider a two- step improvement to be clinically significant. A one-step improvement is within the variation observed with testing. No subject in the no-treatment group improved by 2 steps. In the treatment group 15 out of 21 improved by two steps.*

FST and VA, Modeled Estimates, First Eye (ITT)

Outcome/Parameter	Intervention (N = 21)			Control (N = 10)			Difference (95% CI) (Intervention-Control)	p-value
	Baselin	Year 1	Chang	Baseline	Year 1	Chang		
Full-field light sensitivity testing: white light [Log10(cd.s/m ²)]								
N	20	20	19	9	9	9		
Mean (SE)	-1.23 (0.10)	-3.44 (0.30)	-2.21 (0.30)	-1.65 (0.14)	-1.54 (0.44)	0.12 (0.45)	-2.33 (-3.44, -1.22)	< 0.001
Visual acuity (LogMAR)								
N	21	20	20	10	9	9		
Mean (SE)	1.31 (0.15)	1.14 (0.19)	-0.17 (0.11)	1.37 (0.22)	1.34 (0.28)	-0.03 (0.16)	-0.14 (-0.53, 0.25)	0.46

Column header counts are subjects in the ITT population. *P*-values are presented based on their hierarchical order. All measures are averaged across the first eye

FST and VA, Modeled Estimates, Second Eye (ITT)

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)]								
N	20	20	19	9	9	9		
Mean (SE)	-1.35 (0.09)	-3.28 (0.29)	-1.93 (0.31)	-1.64 (0.14)	-1.69 (0.44)	-0.04 (0.46)	-1.89 (-3.03, -0.75)	0.002
Visual acuity (LogMAR)								
N	21	20	20	10	9	9		
Mean (SE)	1.06 (0.14)	0.91 (0.15)	-0.15 (0.04)	1.21 (0.20)	1.19 (0.21)	-0.02 (0.06)	-0.13 (-0.28, 0.01)	0.072

Reviewer's Comment: *The FST testing is subject to significant bias on the part of the patients due to the subjective nature of the testing and the open label nature of the clinical trial. While the results can be considered supportive of other findings, they do not constitute a demonstration of efficacy. The visual acuity testing is high contrast visual acuity. The visual acuity findings were not supportive of efficacy, but based on the nature of the disease and treatment, high contrast visual acuity would not have been expected to have benefited from treatment. The mobility test measures low light level visual acuity.*

Visual Function Questionnaire Average Scores (ITT)

Parameter/ Visit	Observed				Change from Baseline					
	Intervention N = 21		Control N = 10		Intervention N = 21		Control N = 10			
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Difference (95% CI) (Intervention- Control)	p-value
Average score (subject)										
Baseline	21	4.4 (1.4)	9	4.9 (1.5)						
Day 30	20	6.3 (1.7)	9	4.8 (1.6)	20	1.8 (1.9)	9	-0.1 (0.9)		
Day 90	20	6.7 (1.7)	9	4.8 (1.4)	20	2.3 (1.7)	9	-0.2 (0.9)		
Day 180	20	6.7 (2.1)	9	4.7 (1.3)	20	2.2 (2.0)	9	-0.2 (1.1)		
Year 1	20	7.0 (1.9)	9	5.1 (1.8)	20	2.6 (1.8)	9	0.1 (1.4)	2.4 (1.0, 3.8)	0.001
Average score (parent)										
Baseline	15	3.6 (1.3)	5	3.3 (1.7)						
Day 30	15	6.7 (1.9)	5	3.4 (1.4)	15	3.1 (2.2)	5	0.1 (0.8)		
Day 90	15	6.9 (1.6)	5	3.3 (1.5)	15	3.3 (1.9)	5	0.0 (0.8)		
Day 180 ^a	14	7.3 (1.8)	5	3.4 (1.5)	14	3.5 (2.2)	5	0.2 (1.0)		
Year 1	15	7.5 (1.5)	5	3.1 (1.8)	15	3.9 (1.9)	5	-0.2 (1.3)	4.0 (2.1, 6.0)	0.002

Column header counts are subjects in the ITT population. The observed two-sided *p*-value is from a Wilcoxon rank-sum test.

The Visual Function Questionnaire is not necessarily an accurate measure of subjective visual function and is subject to significant bias on the part of the patients due to the subjective nature of the testing and the open label nature of the clinical trial. While the results can be considered supportive of other findings, they do not constitute a demonstration of efficacy.

Labeling: Multiple rounds of proposed labeling have been exchanged between the applicant and the Agency.

Reviewer's Comment: *I concur with the final labeling, submitted to the Agency during this application cycle.*

Summary Recommendation: I recommend approval of BLA 125610, Luxturna, voretigene neparvovec-rzyl intraocular suspension for subretinal injection for the treatment of patients with confirmed bilallelic RPE65 mutation-associated retinal dystrophy.

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