Clinical Trial Information			
Trial Title	Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis		
Drug(s)/Molecule(s)	voretigene neparvovec;	**Trial Identifier**	GDCT0074523
Secondary ID(s)	NCT00999609; AAV2-hRPE65v2-301;910-1005;302 trial;EudraCT-2016-002109-20;P/221/2015;0910-1005;Study 301;Study 302;AAV2-hRPE65v2-302		
Sponsor (s)	Spark Therapeutics Inc	**Indication**	Leber Congenital Amaurosis (LCA)
Trial Status	Completed	**Trial Phase**	Phase III
Collaborator	Children"s Hospital of Philadelphia;University of Iowa		
Data Monitoring Committee	YES		

Clinical Trial Details	
Trial Title	Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis
Official 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) (AAV2-hRPE65v2-301)
Study Type	Interventional
Therapy Type	Monotherapy
Actual Start Date	01 Oct 2012
Actual End Date	06 Apr 2015
Trial Duration (in Months)	30.57
Study Designs	
Purpose	The purpose of this study was to evaluate the efficacy and safety of the AAV2-hRPE65v2 gene therapy vector as a possible treatment for Leber Congenital Amaurosis (LCA2).
Primary Outcome Measure(s)/Objective(s)	• Multi-luminance Mobility Testing (MLMT), Bilateral - One year (change from baseline) ○ The MLMT measures changes in functional vision, as assessed by the ability to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. MLMT was assessed using both eyes at 1 or more of 7 levels of illumination, ranging from 400 lux (a brightly lit office) to 1 lux (a moonless

	summer night). Each light level was assigned a score code ranging from 0 to 6. A higher score indicated that a subject was able to pass the MLMT at a lower light level. A score of -1 was assigned to those who could not pass MLMT at 400 lux. The MLMT of each subject was videotaped and assessed by independent graders. The MLMT score was determined by the lowest light level at which the subject was able to pass the MLMT. The MLMT score change was defined as the difference between the score at Baseline and the score at Year 1. A positive MLMT score change from Baseline to Year 1 visit indicated that the subject was able to complete the MLMT at a lower light level • The primary endpoint was Multi-Luminance Mobility Test (MLMT) at 7 standard light levels as measured by a change score
Secondary Outcome Measure(s)/Objective(s)	• Full-field Light Sensitivity Threshold (FST) Testing: White Light One year (change from baseline) ((testing rods) and blue and red light (testing cones) o Measures the light sensitivity of the entire visual field by recording the luminance at which a subject reliably reports seeing the dimmest flash • Multi-luminance Mobility Testing (Monocular) One year (change from baseline) o The MLMT measures changes in functional vision, as assessed by the ability to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. MLMT was assessed using the first eye at 1 or more of 7 levels of illumination, ranging from 400 lux (a brightly lit office) to 1 lux (a moonless summer night). Each light level was assigned a score code ranging from 0 to 6. A higher score indicated that a subject was able to pass the MLMT at a lower light level. A score of -1 was assigned to those who could not pass MLMT at 400 lux. The MLMT of each subject was videotaped and assessed by independent graders. The MLMT score was determined by the lowest light level at which the subject was able to pass the MLMT. The MLMT score change was defined as the difference between the score at Baseline and the score at Year 1. A positive MLMT score change from Baseline to Year 1 visit indicated that the subject was able to complete the MLMT at a lower light level. • Measurement of the sharpness of vision, determined by the ability to read letters on a standardized chart from a specified distance • Perceived difficulty of each ADL was reported utilizing a numerical scale from 0 (worst performance/vision) to 10 (best performance/vision), and an

<table>
<tr><td></td><td>average test score was calculated for each time point and for each subject (+/- parent)
• Visual Acuity One year (change from baseline)

o At each visit, subjects and, separately, parents of subjects < age 18 completed a 25-question VFQ adapted for adult and pediatric subjects with inherited retinal disorders and developed to assess vision-dependent activities of daily living (ADL)

Safety endpoints

• Incidence of adverse events and serious adverse events, which were assessed by adverse event recording, routine physical exams and ophthalmic evaluations, and routine laboratory tests such as serum chemistry and hematology
• Immune responses to AAV2 and RPE65, assessed by antibodies to AAV and RPE65, T-cell responses to AAV2 and RPE65 by ELISPOT assay in PBMCs)</td></tr>
<tr><td>Trial Description</td><td>This was an interventional, phase III, randomized, pivotal, registration, controlled, crossover-assignment, open label, parallel-assignment multi-centered and treatment study designed to assess the efficacy and safety of the AAV2-hRPE65v2 gene therapy vector as a possible treatment in subjects with Leber Congenital Amaurosis (LCA2). Subjects were randomized (2:1) into two arms:
<table>
<tr><th>Arm</th><th>Type</th><th>Intervention</th><th>Description</th></tr>
<tr><td>I (n=21)</td><td>Experimental</td><td>AAV2-hRPE65v2</td><td>Subjects received subretinal administration of gene therapy vector AAV2-hRPE65v2 (1.5E11 vector genomes per eye) to both eyes via surgical procedures on separate days</td></tr>
<tr><td>II (n=10)</td><td>Control group</td><td>No Intervention</td><td>Subjects did not receive any intervention</td></tr>
</table>
Two assays were subjected to further validation in-house and used for immune analysis of clinical samples obtained from all intervention subjects.

An Enzyme-Linked Immunosorbent Assay (ELISA) that was capable of detecting a titer of at least 1.55 ug/mL anti-AAV2-capsid human IgG, was done on 21 subjects covering up to four timepoints (baseline before injection, day 30, day 90 and one year). To better evaluate the results, the subjects were placed into six categories based on their antibody titer profile.

The other immunoassay done on the was an interferon-γ Enzyme-Linked Immunospot Assay (ELISPOT) to evaluate the T cell responses against AAV2 capsid or RPE65 transgene product.</td></tr>
</table>

The same set of intervention subjects/timepoints was assessed with positive T cell responses defined as ≥50 spot forming units (SFU) and 3-fold the background (media) control for AAV2 and greater than the statistically determined the cutoff of 161.3 SFU for RPE65.

Intervention group subjects received a subretinal injection of voretigene neparvovec (1.5x1011 vector genomes in a total volume of 300 µL) in one eye and the second eye was injected with the same dose/volume six to 18 days later.

All followed control group subjects crossed over to the intervention group after one year and then received voretigene neparvovec according to the same schedule. **Anti-AAV2 Profile of Intervention Group (n=21)**

Number of Subjects	**Anti AAV Titer Range (ug/mL)**	**Anti-AAV2 Profile**
7	<1.55	Below quantification limit
3	1.72 - 2.91	Low pre-existing antibody titer
2	16.37 - 19.61	Moderate pre-existing antibody titer
4	54.39 - 248.55	High pre-existing antibody titer
4	1.73 - 87.02	Antibody titer developed after vector administration
1	NA	Withdrew

Nine subjects participated in this neuroimaging study. All subjects underwent MRI using a 3T equipped with a 12-channel head coil. Functional and structural MRI were performed at baseline (before intervention), and at 6 months and 1 year post bilateral administration of subretinal gene therapy separated by 10 days. Subjects were randomized to either original intervention (OI:bilateral subretinal VN at baseline; n=20) or delayed intervention (DI:VN after 1 year; n=9). A total of 31 subjects were enrolled in this study.

Trial Notes

As of November 2017, LUXTURNA Priority Review with the U.S. Food and Drug Administration (FDA), with assigned Prescription Drug User Fee Act (PDUFA) expected in January 12, 2018. http://ir.sparktx.com/news-releases/news-release-details/three-year-follow-phase-3-data-provide-additional-information

As per the company presentation at the Jefferies 2016 Global Healthcare Conference, the two-year data (301 trial), crossover data (302 trial) expected to be reported in mid-2016. http://www.jefferies.com/CMSFiles/Jefferies.com/files/Conferences/060716/Presentations/Sparks.pdf As of July 2016, the initial one-year post-administration data from the cross-over subjects (n=9) and the two-year follow-up data from the intervention subjects (n=20) expected in third quarter of 2016. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2

	181454 As per the company presentation at the 34th Annual JP Morgan Healthcare Conference, the cross over data (302 trial) was expected in the second quarter of 2016 and the durability data (301 trial 2 years) was expected in third quarter of 2016. As per the company presentation at the Cowen and Company 35th Annual Healthcare Conference, the trial data expected in the second half of 2015. As of September 2015, database lock was announced for the study and the top-line results for the study were expected to be reported in October 2015. As of November 2014, the trial data expected in second half of 2015. As of May 2014, final data from the trial was expected to be announced in 2015. As of January 2014, trial reached its subjects recruitment goal, total 24 subjects enrolled.

Sponsor(s)/Collaborator(s)	
Sponsor(s)/Collaborator(s) - Type & Details	
Sponsor	Spark Therapeutics Inc (Subsidiary of F. Hoffmann-La Roche Ltd)
Collaborator(s)	Children's Hospital of Philadelphia; University of Iowa

Drug Details

Primary Interventions(s)

Generic Name	Route of Administration
voretigene neparvovec-rzyl	Intraocular

Drug Name	voretigene neparvovec (Pipeline Drug)
Drug Description	Voretigene neparvovec or voretigene neparvovec-rzyl (Luxturna) is an adeno-associated virus vector-based gene therapy. It is formulated as injectable suspension, concentrate for solution for subretinal route of administration. Luxturna is indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy, and also for the treatment of vision loss due to Leber congenital amaurosis or retinitis pigmentosa caused by confirmed biallelic RPE65 mutations. Voretigene neparvovec or voretigene neparvovec-rzyl (Luxturna) is under development for the treatment of choroideremia. It is being developed based on adeno-associated viral (AAV) gene therapy platform.
Mechanism of Action	Voretigene neparvovec acts as retinal pigment epithelium 65 (RPE65) activator. Retinal pigment epithelium 65 gene mutation results in loss of cells in the retina over time which leads to total blindness. The therapeutic candidate improves visual and retinal function by delivering the gene for human RPE65 (AAV2-hRPE65v2-1010) into the RPE. It enables the production of the protein that is

	missing as a result of this genetic mutation.
ATC Classification	S01XA Other ophthalmologicals
Target	Retinoid Isomerohydrolase (All Trans Retinyl Palmitate Hydrolase or Retinal Pigment Epithelium Specific 65 kDa Protein or Retinol Isomerase or RPE65 or EC 3.1.1.64)
Drug Name	voretigene neparvovec (Marketed Drug)
Mechanism of Action	Voretigene neparvovec acts as retinal pigment epithelium 65 (RPE65) activator. Retinal pigment epithelium 65 gene mutation results in loss of cells in the retina over time which leads to total blindness. The therapeutic candidate improves visual and retinal function by delivering the gene for human RPE65 (AAV2-hRPE65v2-1010) into the RPE. It enables the production of the protein that is missing as a result of this genetic mutation.
ATC Classification	S01XA Other ophthalmologicals
Target	Retinoid Isomerohydrolase (All Trans Retinyl Palmitate Hydrolase or Retinal Pigment Epithelium Specific 65 kDa Protein or Retinol Isomerase or RPE65 or EC 3.1.1.64)

Patient Details

Age	**Minimum Age Eligibility**: 3 Years **Maximum Age Eligibility**:
Gender	Both
Healthy Subject(s)	No
Subject(s) Type	Adolescents, Adults, Children, Elders, RPE65 Mutation
Participant Criteria (Inclusion)	• 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 biallelic 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 ○ An area of retina within the posterior pole of >100 µm thickness shown on OCT

	○ Greater than or equal to 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or ○ 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 ○ 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
Participant Criteria (Exclusion)	• 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 • Subjects with insufficient viable retinal cells as determined by optical coherence tomography (OCT), e.g., areas of retina with thickness measurements less than 100 µm, or absence of neural retina

Ethnicity	
Hispanic/Latino	6
Not Hispanic/Latino	25

Race	
American Indian/Alaska Native	3
Asian	5
Black/African American	2
White	21

Biomarker Details

Biomarker Name	Biomarker Identifier	Biomarker Official Symbol	Biomarker Role
Interferon Gamma	GDBM0000808	IFNG	Monitoring Treatment Response
Retinoid Isomerohydrolase RPE65	GDBM0007953	RPE65	Inclusion criteria; Monitoring Treatment Response

Trial Results	
No. of Subjects Planned	27
No. of Subjects Enrolled	31

No. of Subjects Analyzed	31
Endpoint Classification	Efficacy, Safety
End Point Status	Achieved
Efficacy Results	**February 10, 2023** Taiwan Food and Drug Administration (TFDA) Assessment Report of Luxturna_concentrate_and_solvent_for_solution_for_injection Based on the results reported, GlobalData inferred that efficacy analysis was performed in this study. For the ITT population, the mean multi-luminance mobility test (MLMT) change score was 1.8 for the Intervention group and 0.2 for the Control group, resulting in a mean difference (95% CI) of 1.6 (0.72, 2.41). This MLMT change score difference was statistically significant (p=0.001) from both the observed and permutation test p-values. Similar results were observed for the mITT (1.6 [0.76, 2.50]; p=0.004) and PP (1.7 [0.79, 2.56]; p=0.004) analysis populations. For the ITT population, analysis of the FST results averaged over both eyes showed a mean change from Baseline to Year 1 of -2.08 log10 (cd.s/m2) for the Intervention group and 0.04 log10 (cd.s/m2) for the Control group, for a statistically significant (p < 0.001) between-group mean (95% CI) treatment difference of -2.11 (-3.19, -1.04) log10 (cd.s/m2). For the monocular MLMT change score for the first-treated eye, the mean change from Baseline to Year 1 was 1.9 for the Intervention group and 0.2 for the Control group, resulting in a statistically significant (p=0.001) mean (95% CI) treatment difference of 1.7 (0.89, 2.52). Analysis of visual acuity averaged over both eyes showed a mean change from Baseline to Year 1 of -0.16 LogMAR for the Intervention group and 0.01 LogMAR for the Control group, resulting in a non-significant (p=0.17) mean (95% CI) treatment difference of -0.16 (-0.41, 0.08). https://www.fda.gov.tw/tc/includes/GetFile.ashx?mid=189&id=42534&t=s **September 03, 2022** Presented at the 22nd Virtual Annual Congress of The European Society of Retina Specialists (EURETINA 2022), September 01 - 04, 2022, Hamburg, Germany Voretigene Neparvovec Exploratory Analysis (VNEAN): R-shiny App for the Comprehensive and Dynamic Visualization of Voretigene Neparvovec Clinical Trial Data Session: Inherited Retinal Diseases Iryna Lobach et al.Based on the results presented, GlobalData inferred that an interactive and dynamic application (VNEAN) was developed. VNEAN app has 11 modules of data analyses, including longitudinal visualization, analyses of correlation between changes, and timeline of adverse events. It has the potential to provide alternative data visualization and interpretations of analyses that offer a comprehensive

representation of the data generated in rare diseases, not easily achievable via traditional didactic lectures and static data methods. https://euretina.softr.app/abstract?recordId=reco0qS5eixiKHFRi

December 15, 2020 Therapeutic Goods Administration (TGA) Australian Public Assessment Report (AusPAR) for Voretigene neparvovec (Luxturna) Based on the results reported, GlobalData inferred that efficacy analysis was performed in this study. The mean and SD bilateral MLMT change score for Year 1 compared to Baseline was 1.8 (1.1) and 0.2 (1.0) for the intervention and control groups respectively; with a mean difference (intervention versus control) of 1.6 (95% confidence interval (CI): 0.72, 2.41; p = 0.001). The median MLMT change score was 2 in the intervention group and 0 in the control group. The mean and standard deviation (SD) FST score for white light was -1.29 (0.09) and -1.65 (0.14) log10 candela second per metre squared (cd.s/m2) in the intervention and control group respectively at Baseline. The mean visual activity at Baseline was 1.18 logMAR in the intervention group (range 0.72 to 2.17), and 1.29 in the control group (range 0.51 to 4). https://www.tga.gov.au/sites/default/files/auspar-voretigene-neparvovec-201215.pdf (16,17) **December 15, 2020** Therapeutic Goods Administration (TGA)
Voretigene neparvovec (Luxturna) - Product Information Based on the results reported, GlobalData inferred that efficacy analysis was performed in this study.
Changes in MLMT score: Year 1, compared to baseline :

Change in MLMT score	**Difference (95% CI) Intervention-Control**	**p-value**
using binocular vision	1.6 (0.72, 2.41)	0.001
using assigned first eye only	1.7 (0.89, 2.52)	0.001
using assigned second eye only	2.0 (1.14, 2.85)	<0.001

https://www.tga.gov.au/sites/default/files/auspar-voretigene-neparvovec-201215-pi.pdf (16) **December 16, 2017** U. S. Food and Drug Administration (FDA) – Center for Drug Evaluation and Research (CDER)
Luxturna (Voretigene neparvovec) – Clinical Review Based on the results reported, GlobalData inferred that efficacy analysis was performed in this study.
MLMT Score Change at Year 1 (ITT):

MLMT Score Change	**Treatment (N=21)**	**Control (N=10)**	**p-value**
Both eyes			
Mean (SD)	1.8 (1.1)	0.2 (1.0)	
Quartiles (QI, Median, Q3)	1, 2, 3	-1, 0, 1	0.001

Range (min, max)	0, 4	-1, 2	
First-Treated Eye			
Mean (SD)	1.9 (1.2)	0.2 (0.6)	
Quartiles (Q1, Median, Q3)	1, 2, 3	0, 0, 1	0.0
Range (min, max)	0, 4	-1, 1	-

https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Clinical-Review--December-16--2017---LUXTURNA.pdf (54) **July 29, 2017** European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP)
Public Assessment Report of Luxturna (Voretigene neparvovec) Based on the results reported, GlobalData inferred that efficacy analysis was performed in this study. **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 p-valve**	**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			

https://www.ema.europa.eu/en/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf (34) **October 05, 2015** Foundation Fighting Blindness Applauds Phase 3 Study Results for Investigational Gene Therapy Treatment Based on the top-line results reported, GlobalData inferred that the study met the primary endpoint.

Functional vision improvement, as measured by the change in bi-lateral mobility testing from baseline to one year, was observed in subjects receiving SPK-RPE65 compared to the control group subjects.
http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2093863 **October 10, 2015** Spark Therapeutics Announces Presentation of Additional Phase 3 and Durability Data on SPK-RPE65 at The Retina Society 48th Annual Scientific Meeting Based on the results announced by Spark Therapeutics, Inc. in the press release, GlobalData inferred that a total of 31 subjects (ITT population) were randomized in the study, 21 in intervention group and 10 in the control group. A total of 29 subjects, includes all subjects that received SPK-RPR65 and only those who continued beyond the baseline study visit, were included in the study (mITT population). **Findings:**

Functional vision	**Experimental (AAV2-**	**Control**

	hRPE65v2) subjects	subjects
Mobility testing, specified lux levels	1.9	0.2
Full-field light sensitivity threshold testing (FST), log10 (candela second/m^2)	-2.06	0.04

In modified intent-to-treat (mITT) population, a little more improvement in the functional vision, as measured by the change in bilateral mobility testing (MT) between baseline and one year was observed in intervention subjects compared with control subjects. In intervention subjects, 13 subjects receiving SPK-RPR65 who were able to pass MT at one lux at year one, showed maximum improvement on the MT score, but no one of the control subjects was able to pass MT. **Findings:**

Parameter	p-Value, In ITTpopulation
MT change score, bilateral	0.001
FST, averaged over both eyes	0.001
MT change score, first injected eye	0.001
VA, averaged over both eyes	0.17

By FST for white light, a highly statistically significant mean improvement was observed in intervention subjects compared with decline among control subjects in mITT population. It was observed that throughout the entire one-year study period, significant differences both MT and FST was observed by the first study visit, at 30 days and these effects were re observed at days 90, 180 and one year. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle_print&ID=2095955 **January 11, 2016**

Presented at the 34th Annual JP Morgan Healthcare Conference, January 11-14, 2016, California, USA

Based on the results presented, GlobalData inferred that improvement in mean mobility test score was observed in 65% subjects with mean 100 % fold improvememt in light sensitivity. SPK-RPE65 demonstrated statistical significance in visual acuity analysis. According to Lange scale, treatment group was observed with nine letter average improvement compared with the control group (1.6) (p=0.047). In sub group analysis, after removal of subjects with cataracts (n=3) average improvement in the endearment group was 10.6 letters compared to placebo (1.6) (p=0.007). In accordance with SAP, statistical significance was not achieved with visual acuity (p=0.17). Unfavorable immune responses were not observed during the study. http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjA2NjY0fENoaWxkSUQ9MzE5MDgwfFR5cGU9MQ==&t=1 (Slides 03, 04, 10, 11, 12, 13, 23) **May 04, 2016**
Presented at the 19th American Society of Gene and Cell Therapy (ASGCT) Annual Meeting, May 04-07, 2016, Washington, DC 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
Session: Gene Therapy for Neurosensory Diseases
Abstract no.: 185 Daniel J Hui et al. Based on the results presented, GlobalData inferred that a total of 21 subjects were analyzed in this study. Eighteen subjects were tested negative for T cell responses against AAV2 and RPE65 across all time-points. Only one subject was tested positive against AAV2 capsid at baseline (55.0 SFU) and against RPE65 at the one year time-point (171.7 SFU). At one year, another subject tested positive against RPE65 only (170.0 SFU).

All these positive responses were weak with respect to cutoff values at threshold. Moderate response was seen in one subject (518.3 SFU) against RPE65 at baseline only, while all the subsequent timepoints were negative.

The positive T cell responses that were observed at baseline before the administration of vector were unlikely to be related to gene transfer.
http://www.abstractsonline.com/pp8/#!/4077/presentation/165 **November 14, 2015** Spark Therapeutics Announces Presentation of Additional Phase 3 Data on SPK-RPE65 at The American Academy of Ophthalmology 2015 Annual Meeting
Based on the results announced by the Spark Therapeutics, in the press release, GlobalData inferred that SPK-RPE65 treatment demonstrated a highly statistically significant improvement as compared to control group.

Primary outcome (ITT)	**p- Value**
MT change score, bilateral	0.001
Secondary outcomes (ITT)	
FST, averaged over both eyes	<0.001
MT change score, assigned first eye	0.001
VA, averaged over both eyes	0.17

The change in bilateral mobility testing (MT) and full-field light sensitivity threshold testing (FST) and MT for the assigned first eye showed statistically significant improvements between baseline and one year. Modified intent-to-treat efficacy analysis subjects achieved a mean improvement of two lines (9.0 letters averaged across both eyes) on the angle of resolution (logMAR) scale, as compared to slight improvement (1.6 letters) in control subjects. Seven of 20 one-third saw a 15-letter, or three-line, improvement in the first eye administered, as compared with none in the control group. In the second eye, four of 20 intervention subjects reached a 15-letter improvement as compared with control subjects. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2112455 **March 09, 2016** Spark Therapeutics Reports 2015 Financial Results and Business Highlights Based on the results announced by the Spark Therapeutics in the press release, GlobalData inferred that the SPK-RPE65 resulted a substantial restoration of functional vision with approximately two-thirds of the subjects in the intervention group achieving the maximum improvement measurable on the mobility test.

http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2147143 **November 04, 2015** Spark Therapeutics Reports Third Quarter 2015 Financial Results and Recent Business Highlights Based on the results announced by the Spark Therapeutics, in the press release, GlobalData inferred that the study met its primary endpoint.

Parameters	**p-Value**
Bilateral mobility test (MT) change score	0.001
Full field light sensitivity threshold testing score	<0.001
First eye MT change score	0.001

About thirteen out of the 20 subjects receiving SPK-RPE65 achieved the maximum improvement measurable on the mobility test. SPK-RPE65 improved approximately 100-fold in light sensitivity on average as compared to control group. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2106466 **October 09, 2015** Gene Therapies Move One Step Closer to Reality Based on the results announced by the Spark Therapeutics, in the press release, GlobalData inferred that the treated group out performed control subjects across the first two secondary endpoints during the treatment. http://ois.net/gene-therapies-move-one-step-closer-to-reality/ **June 10, 2016** Presented at the Jefferies 2016 Healthcare Conference, June 07-10, 2016, New York, US Based on the results presented, GlobalData inferred that a statistical and clinically remarkable durability of benefit demonstrated by voretigene neparvovec for over three years in this study. http://www.jefferies.com/CMSFiles/Jefferies.com/files/Conferences/060716/Presentations/Sparks.pdf **August 10, 2016** Spark Therapeutics Announces New Positive Data from Continuation of Phase 3 Trial of Voretigene Neparvovec Based on the results announced by Spark Therapeutics, Inc. in the press release, GlobalData inferred that the follow-up data had shown a two-year durability of benefit in the intervention group. There were 27/29 (93%) subjects exhibited a gain in the functional vision at one-year. Among the nine crossover subjects, eight responders had shown the maximum improvement measurable on the primary endpoint at one-year. The mean improvement among all nine subjects was 2.1 lux levels when compared to the 1.9 lux level improvement in group of 20 subjects. On FST testing, 8/9 subjects had shown an improvement with an average improvement of nearly 200-fold when compared to the more than 100-fold improvement average in study subjects. Subjects in this study had shown an average visual acuity improvement of 4.5 letters, averaged across the both eyes when compared to an average improvement of eight letters by same analysis in this study. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2194535 **August 10, 2016** Spark Therapeutics Reports Second Quarter 2016 Financial Results and Recent Business Highlights Based on the results announced by Spark Therapeutics in the press release, GlobalData inferred that maximum improvement measurable on the bilateral mobility test was observed in the eight responders among the nine cross over subjects during the study.

http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2194546

September 09, 2016 Presented at the 16th EURETINA Congress 2016, September 8-11, Bella Center, Copenhagen, Denmark Phase 3 efficacy and safety study of voretigene neparvovec (AAV2hRPE65v2) in subjects with RPE65 mediated inherited retinal dystrophy
Free Paper Session 18: New Drug Treatment and Technology 1 Leroy B et al. Based on the results presented, GlobalData inferred that improvement in multiluminance mobility test (MLMT) was achieved by 30 days and remained stable through one year.

Parameters	**Intervention group**	**Control group**	**p-Value**
MLMT change score at 1 year	1.8 ± 1.1	0.2 ± 1.0	0.001
Bestcorrected visual acuity (BCVA), letters	9	1.6	0.035

At 1 year, 65% of those receiving voretigene neparvovec in the intervention group and no subjects in the control group, passed multiluminance mobility test at the lowest luminance level tested (1 lux) reporting the maximum MLMT improvement. Improvements in MLMT was observed only the first assigned eye were similar and also highly statistically significant (p=0.001).

Mean full-field light sensitivity threshold testing (FST) demonstrated a >100 fold improvement in white light sensitivity by day 30 in the intervention group, which remained stable through one year compared no meaningful change in the control group (p<0.001). Bestcorrected visual acuity (BCVA) demonstrated a numerical improvement between the control groups and intervention, but the difference was not statistically significant (p=0.17).

http://euretina.org/copenhagen2016/programme/free-papers-details.asp?id=4657&day=0 **November 03, 2016** Spark Therapeutics Reports Third Quarter 2016 Financial Results and Recent Business Highlights Based on the results announced by Spark Therapeutics, in the press release, GlobalData inferred that during the pivotal controlled portion of the study, statistically significant results for visual field (VF) were observed. VF increased from baseline at year one for the intervention group, whereas decreased at year one for the control group, with a positive difference of 387.7 sum total degrees. Similarly VF increased from baseline at year one for the intervention group and decrease at year one for the control group. Efficacy results which were observed in the initial first year of the trial were reinforced in the crossover group and were maintained for an additional year of follow-up in the original intervention group. **Outcomes:**

Parameter	**Intervention group**	**Control group**	**p-Value**

Periphery visual field (VF) using the Goldmann III4e test stimulus	302.1	76.7	0.006
VF from baseline at year one using the Humphrey macula threshold measure, decibels	7.7	0.2	0.001

http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2219135 **January 10, 2017**

Presented at the 35th Annual J.P. Morgan Healthcare Conference, January 09-11, 2017, San Fransisco, California, USA

Based on the results presented, GlobalData inferred that a total of 72% subjects were observed with maximum improvement with voretigene during the study. Average improvement of more than150 in light sensitivity was observed during the study. http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjU2NjIwfENoaWxkSUQ9MzYzMjU1fFR5cGU9MQ==&t=1 (Page 03, 07, 08,09,10,12) **February 15, 2017** 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) (AAV2-hRPE65v2-301) Based on the results presented, GlobalData inferred that a total of 31 subjects were analyzed during the study.

Parameter	**Treatment**	**Control**
Mobility Testing	1.8 ± 1.1	0.2 ± 1
Full-field light sensitivity threshold	-2.08 ± 0.29	0.04 ± 0.44
Monocular Mobility Testing	1.9 ± 1.2	0.2 ± 0.6
Visual Acuity	-0.16 ± 0.07	0.01 ± 0.1

https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002109-20/results **March 26, 2018**

Safety and Efficacy Study in Subjects With Leber Congenital Amaurosis

Based on the study results reported, GlobalData inferred that a total of 31 subjects were analyzed in the study.

	Intervention	**Control**
Participants Analyzed	21	10
Multi-luminance Mobility Testing (MLMT), Bilateral	1.8 (1.1)	0.2 (1.0)

https://clinicaltrials.gov/ct2/show/results/NCT00999609?sect=X70156 **March 06, 2017** Presented at the 37th Cowen and Company Annual Health Care Conference, March 06-08, 2017, Boston, Massachusetts, USA Based on the results presented, GlobalData inferred that the functional vision was observed to be significantly impaired at baseline.

phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjYyMjg0fENoaWxkSUQ9MzY5NDAzfFR5cGU9MQ==&t=1 (Slides 03,07,08, 09,10,12) **May 10, 2017**

Presented at the Association for Research in Vision and Ophthalmology's (ARVO) 2017 Annual Meeting, May 07 - 11, 2017, Baltimore, MD, USA

Year 2 results for a phase 3 trial of voretigene neparvovec in biallelic RPE65 - mediated inherited retinal disease
Session 424 Drug and gene therapy and delivery
Program No.: 4122
Poster Board No.: B0122

Stephen R Russell et al.

Based on the results presented, GlobalData inferred that a total of 29 subjects were analyzed in this study.

Parameter	**Orignal Intervention groupat 2 years**	**Delayed intervention (DI) group at 1 year**
Change in white light FST, log 10 (cd.s/m^2)	-2.27 (1.65)	-2.86 (1.49)
Holladay VA, letter gain	7.8 (-0.16 logMAR, SD 0.36)	4.5 (-0.09 logMAR, SD 0.22)
Mean change in sum total degrees on GVF III4e	311.6 (SD 295.3)	194.3 (SD 244.7)
Change in HVF macula threshold averaged over both eyes, db gain	6.45 (SD 7.35)	5.23 (SD 9.92)

A trend toward improved Holladay VA averaged over both eyes was seen.

http://www.arvo.org/webs/am2017/sectionpdf/PH/Session%20424%20Drug%20and%20gene%20therapy%20and%20delivery.pdf (Page 21) **May 09, 2017**

Presented at the Association for Research in Vision and Ophthalmology's (ARVO) 2017 Annual Meeting, May 07 - 11, 2017, Baltimore, MD, USA

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
Session 344 Functioning with low vision
Program No.:3292
Poster Board Number: B0425

Daniel C Chung et al.

Based on the results presented, GlobalData inferred that correlation between multiluminance mobility test bilateral change score percentage max and full-field light sensitivity threshold was reported as -0.74. The correlations between multiluminance mobility test bilateral change score percentage max and humphrey visual field foveal sensitivity and multiluminance mobility test bilateral change score percentage max and humphrey visual field macula threshold were reported as 0.66 and 0.63, respectively (each p<0.001). www.arvo.org/webs/am2017/sectionpdf/LV/Session%20344%20Functioning%20with%20Low%20Vision.pdf (Page 13) **June 2017** Spark Therapeutics Inc. Corporate Presentation Based on the results presented, GlobalData inferred that the gain in functional vision based on MLMT was observed in 93% (27/29) of subjects at one-year with 72% maximum improvement achieved with 1 lux in this study. phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjY1OTEzfENoaWxkSUQ9MzgxMTUwfFR5cGU9MQ==&t=1 (Slides 03,04,07,08,09,10,21) **July 13, 2017**

Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial

Stephen Russell et al.

The Lancet, 2017

Based on the results published, GlobalData inferred that a total of 29 subjects were analyzed in this study.

In an intervention subjects but no control subjects passed MLMT at the lowest luminance level tested (1 lux) which demonstrating maximum possible improvement.

Parameter	**Intervention group**	**Control group**	**Difference, (95% CI)**	**p-value**
mean bilateral MLMT change score at 1 year, light levels (SD)	1·8 (1·1)	0·2 (1·0)	1·6 (0·72–2·41)	0·0013
Passed MLMT at the lowest luminance level tested (1 lux), light levels (SD)	1·8 (1·1)	0	-	-

	http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31868-8/abstract **July 13, 2017** Spark Therapeutics Announces Publication in The Lancet of Pivotal Phase 3 Clinical Trial Data for Investigational Voretigene Neparvovec Based on the results announced by Spark Therapeutics, Inc., in the press release, GlobalData inferred that clinically meaningful and statistically significant were observed difference between intervention (n=21) and control subjects(n=10) at one year, per the clinical trial's primary endpoint. Subjects maintained functional gains seen 30 days post-administration at the one year primary endpoint. In MLMT improvements seen were accompanied by statistically significant improvements in two secondary endpoints which including full field light sensitivity threshold (FST) testing mean over both eyes (p=0.0004). In a third secondary endpoint, the change in visual acuity mean over both eyes, statistically not significant between intervention and control subjects (p=0.17). In an additional protocol-specified endpoint, the visual field area of the original intervention group demonstrated significant improvement (p=0.0059), nearly twice at year one, while a slight decrease was seen in the control group over the same time period. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2286471 **July 17, 2017** Spark Therapeutics' Biologics License Application for Investigational Voretigene Neparvovec Accepted for Filing by FDA Based on the results announced by Spark Therapeutics in the press release, GlobalData inferred that the primary endpoint, mean bilateral multi-luminance mobility testing (MLMT) change score was significantly different between intervention (n=21) and control participants (n=10) at one year (difference of 1.6; 95% CI, 0.72, 2.41; p=0.001). http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2286691 **July 31, 2017** Spark Therapeutics Submits Marketing Authorization Application to European Medicines Agency for Investigational LUXTURNA (voretigene neparvovec) Based on the results reported by Spark Therapeutics, in the press release, GlobalData inferred that a marked difference was observed in subjects between the experimental and control arms for the secondary end point- mobility testing for the first injected eye with a score of p=0.0005. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2290110 **September 06, 2017** Spark Therapeutics Inc Corporate presentation Based on the results reported GlobalData inferred that

	greater than 150 fold average improvement in light sensitivity was observed.Visual acuity did not reach statistical significance 9 letter improvement (p=0.17) was observed. Visual Field (VF) was improved by two measures with a near doubling in Goldmann VF. phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9Njc3MDEwfENoaWxkSUQ9Mzg4MTM0fFR5cGU9MQ==&t=1 **October 12, 2017** Spark TherapeuticsSpark Therapeutics (ONCE) Trading of Stock Halted as FDA Advisory Committee Reviews Investigational Gene Therapy Based on the results announced by Spark Therapeutics in the press release, GlobalData inferred that a total of 72% of subjects successfully completed MLMT at the lowest light level evaluated at one year after voretigene neparvovec treatment. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&cat=news&id=2306224 **November 14, 2017** Presented at the American Academy of Ophthalmology (AAO) Annual Meeting 2016, November 11-14, 2017, New Orleans, LA, United States Phase 3 Trial Update of Voretigene Neparvovec in Biallelic RPE65-Mediated Inherited Retinal Disease Session: Paper Abstract No.: PA095 Stephen Richard Russell et al. Based on the results presented, GlobalData inferred that the multiluminance mobility test mean (SD) bilateral change score was 1.9 (1.1) levels for Voretigene Neparvovec treated subjects (n = 20) at 2 years and 2.1 (1.6) for control subjects (n = 9) at 1 year. About 89% of control subjects passed MLMT at the lowest light level, 1 lux. The mean change (cd.s/m^2) in white light FST on averaging for both eyes was −2.27 $\log_{10}$ (1.65) at 2 years fortreatment arm and −2.86 (1.49) at 1 year for control arm, the latter a □180% light sensitivity increase. https://secure.aao.org/aao/meeting-archive **December 19, 2017** FDA Approves Spark Therapeutics' LUXTURNA (voretigene neparvovec-rzyl), a One-time Gene Therapy for Patients with Confirmed Biallelic RPE65 Mutation-associated Retinal Dystrophy Based on the results announced by Spark Therapeutics in Press release, GlobalData inferred that there was a significant difference between both arms for the median bilateral MLMT score change (treatment-control group difference : 2; p=0.001) and median first-treated eye MLMT score change (treatment-control group difference : 2;; p=0.003) at one year. After cross over subjects of the control arm showed a similar response to treatment arm. The intervention group showed median bilateral MLMT score change of two at the 30-day timepoint and was sustained for at least three years for the original treatment arm na dtwo years for the crossover group. Intervention treated subjects showed a significant improvement from baseline to one year in white light FST. There was no significant difference in change in visual acuity from baseline to one year between arms. http://ir.sparktx.com/news-releases/news-release-details/fda-approves-spark-therapeutics-luxturnatm-voretigene-neparvovec **May 01, 2018** Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2018), Apr 29 - May 03, 2018, Honolulu, Hawaii, USA Three-year update for the phase 3 voretigene neparvovec study in biallelic RPE65 mutation–associated inherited retinal disease Session: Profound Low Vision and Low-vision Clinical Trials

	Abstract No.: 3900 - C0366 Stephen R Russell et al. Based on the results presented, GlobalData inferred that a total of 29 subjects were analyzed in this study. Multi-luminance mobility test mean (SD) bilateral score change was 1.8 levels (1.0) for intervention subjects (n=20) at three years and 2.1 levels (1.6) for control/intervention subjects (n=9) at two years with >70% of all subjects are able to pass multi-luminance mobility test at the lowest light level measured at three years in intervention subjects) and two years in control/intervention subjects. Mean change in white light full-field light sensitivity threshold averaged over both eyes were -2.04 log10 (cd.s/m2) (1.43) at three years for intervention subjects (n=19) and -2.69 log10 (cd.s/m2) (1.41) at two years for control/intervention subjects (n=9). Improvements in FST was >150-fold in light sensitivity for all the subjects measured at three years in intervention subjects and two years in control/intervention subjects. Mean change (SD) in visual acuity averaged over both eyes were consistent through three years for intervention subjects and two years for control/intervention subjects. The mean change (SD) in sum total degrees on goldmann kinetic visual field (GVF) III4e, averaged over both eyes were 282 (257) for intervention subjects at three years and 183 (310) in control/intervention subjects at two years. https://ep70.eventpilot.us/web/page.php?page=IntHtml&project=ARVO18&id=2915552 **May 16, 2018** Presented at the 21st American Society of Gene and Cell Therapy (ASGCT) Annual Meeting, May 16-19, 2018, Chicago, Illinois, USA Assessment of Bilateral Retinal Gene Therapy of the Phase 3 LCA2 Clinical Trial: A Longitudinal fMRI Study of Binocular Visual Functions Session: Neurologic Diseases (Including Ophthalmic and Auditory Diseases) I Abtsract No: 291 Mariel A Salkeld etal. Based on the results presented, GlobalData inferred that a total of nine subjects were analyzed in the study. The averaged brain responses increased from baseline to one year after LCA2 subejcts received bilateral retinal gene therapy. The rate of increase for the areas of activations distributed in the left and right hemispheres were 40% and 20% for total visual cortex and the medial aspects, respectively. The preliminary group fMRI results demonstrated that the efficacy of Luxturna to reinstate vision in a group of LCA2 subjects. The subjects showed lower levels of cortical activations at baseline and after receiving retinal gene therapy, they presented significant increased levels of cortical activation at six months and one year. The fMRI results were indicative of the fact that the visual pathway in LCA2 subjects remain responsive to visual stimulation once the remaining viable photoreceptors are restored through GT. https://plan.core-apps.com/asgct2018/abstract/c3f26eef-44bb-455c-96fc-2561e734e2c7 **September 14, 2018** Presented at the 51st Scientific Meeting of The Retina Society Annual meeting 2018, September 12 - 15, 2018, San Francisco,

	California Three-year Update for the Phase 3 Voretigene Neparvovec-rzyl Study in Biallelic RPE65 Mutation–Associated Inherited Retinal Disease Session: Genetics Diseases, Dystrophies and Degenerations Thomas ciulla et al, Based on the results presented, GlobalData inferred that voretigene neparvovec-rzyl showed favorable profile with improved functional vision and visual function in subjects with biallelic *RPE65* mutation associated inherited retinal disease for least 3 years after treatment. Improved multi-luminance mobility test (MLMT), Goldmann kinetic VF, full-field light sensitivity threshold was observed in subjects. https://www.xcdsystem.com/retinasociety/program/ldA8aA9/index.cfm?pgid=21&SearchTerm= **September 22, 2018** Presented at the 18th Congress of The European Society of Retina Specialists (EURETINA 2018), September 20-23, 2018, Vienna, Austria Year 1 time to mobility test completion in a voretigene neparvovec trial in subjects with RPE65 mutation–associated inherited retinal disease Session: Free Paper Session 18: New Drug Treatment & Technology II LeRoy B et al. Based on the results presented, GlobalData inferred that 29 subjects were analyzed in the study. Subjects with voretigene neparvovec reported shorter time to complete the MLMT compared to control subjects except the lowest passing baseline lux level not adjusting for multiplicity for all analyses were P<0.05. http://www.euretina.org/congress/vienna-2018/vienna-2018-abstracts/?title=Free%20Paper%20Session%2018:%20New%20Drug%20Treatment%20&%20Technology%20II&sessiom=740&title=Free%20Paper%20Session%2018:%20New%20Drug%20Treatment%20&%20Technology%20II **September 21, 2018** Presented at the 18th Congress of The European Society of Retina Specialists (EURETINA 2018), September 20-23, 2018, Vienna, Austria Year 3 results and agestratified analyses for a phase 3 trial of voretigene neparvovec in RPE65 mutation–associated inherited retinal disease Session: Free Paper Session 11: New Drug Treatment & Technology I LeRoy B et al. Based on the results presented, GlobalData inferred that the crossover control group shown similar endpoints after treatment at year two to that of year one original intervention group and the original intervention endpoints observed were maintained through year three. MLMT year three original intervention change observed was 1.8 (1.0) and for year two crossover control was 2.1 (1.6). Visual acuity year three original invention improvement observed was − 0.16 (0.35) log MAR (~8 letters) and for year two crossover control observed was − 0.06 (0.23) (~3 letters). Goldmann VF III4e monocular sum total degree at year three original intervention mean change observed was 282.2 (256.5) and for year 2 crossover control 182.6 (309.9). Significant difference was not observed between subjects < or ≥ 10 years for MLMT, FST, GVF, or VA at one year posttreatment (Posthoc, p - 0.54, 0.98, 0.94, 0.084).

	http://www.euretina.org/congress/vienna-2018/vienna-2018-abstracts/?title=Free%20Paper%20Session%2011:%20New%20Drug%20Treatment%20&%20Technology%20I&sessiom=733&title=Free%20Paper%20Session%2011:%20New%20Drug%20Treatment%20&%20Technology%20I **October 29, 2018** Spark Therapeutics Presents Three Post-hoc Analyses from Phase 3 Clinical Trial of LUXTURNA (voretigene neparvovec-rzyl) at American Academy of Ophthalmology Annual Meeting Based on the results from three post-hoc analyses announced by Spark Therapeutics Inc., in the press release, GlobalData inferred that improvement in best-corrected (with optimal glasses/contact lens prescription) visual acuity averaged over both eyes for subjects receiving voretigene neparvovec-rzyl and was not statistically significant when compared to the control group (p=0.17) at year one. In this post-hoc analysis, visual acuity data were revisited using the Lange method and at year one using this method showed a statistically significant improvement from baseline in subjects receiving voretigene neparvovec-rzyl when compared to control group in best-corrected visual acuity averaged over both eyes (nominal p<0.05). Among subjects who receivied LUXTURNA, 25/29 reported unique genotypes were characterized into subtypes based on both the mutation type and the likeliness of pathogenicity. Correlations were not found between RPE65 mutation subtype and baseline visual function or treatment response. Improvements in the function of retinal cone cells were observed in the study. Statstically significant improvements in the mean values averaged over both eyes for white light FST testing that assesses rod function, blue light FST testing that assesses rod and cone function and red light FST testing that assesses cone function were observed from baseline when compared to the control group at year one (p<0.001, nominal p=0.002 and nominal p<0.001, respectively). The improvements in rods were greater than in cones. http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-presents-three-post-hoc-analyses-phase-3 **October 28, 2018** Presented at the American Academy of Ophthalmology (AAO) Annual Meeting 2018, October 27-30, 2018, Chicago, United Statesany RPE65 Mutation Subtype Effects on Baseline Visual Function and Treatment Response in Phase 3 Voretigene Neparvovec Trial Session: Retina, Vitreous Abstract No.: PO220 Vinit Mahajan et al. Based on the results presented, GlobalData inferred that the eight of 29 subjects had homozygous mutations and 21 had heterozygous and 34 individual genetic mutations were reported. Apparent association was not observed between genetic mutation and baseline visual function, treatment response, or adverse events. The benefit/risk profile of voretigene neparvovec (VN) was not predicted by mutation subtype. Therefore, inherited retinal dystrophy (IRD) subjects with any combination of biallelic *RPE65* mutations considered for VN treatment. https://secure.aao.org/aao/meeting-archive **October 28, 2018** Presented at the 2018 Annual Meeting of the American Academy of Ophthalmology (AAO 2018), October 27-30, 2018, Chicago, Illinois, United States

Cone-Mediated Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial
Session: Retina, Vitreous
Abstract No.: PO225

Julia A Haller et al.

Based on the results presented, GlobalData inferred that 31 subjects were analyzed in the study.

Parameters	**Observations (log10(cd.s/m2))**	**Difference (95% CI)**	**P value**
White light FST Year 1 mean change (mITT)	−2.06 and 0.04	−2.10(−3.18 to −1.02)	< .001
Blue light FST Year 1 mean change	−1.96 and 0.13	−2.09 (−3.32 to −0.86)	.002
Red light mean change	−1.29 and 0.16	−1.45 (−2.05 to −0.85	< .001

https://secure.aao.org/aao/meeting-archive **October 29, 2018** Presented at the 2018 Annual Meeting of the American Academy of Ophthalmology (AAO 2018), October 27-30, 2018, Chicago, Illinois, United States Visual Acuity Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial
Session: Retina, Vitreous
Abstract No.: PA074 Albert M Maguire et al. Based on the results presented, GlobalData inferred that a total of 29 subjects were analyzed in this study. At one-year study the mean BCVA improvements (mITT) were averaged over both eyes was 9.0 letters (intervention, n = 20) versus 1.6 letters (control, n = 9) (difference 7.4 letters; 95% CI- 0.1-14.6, p=0.0469). Improvements of the logMAR 0.3-equivalent to three-line improvements and considered clinically meaningful observed in 50% (10/20) of intervention first treated eyes and in 20% (4/20) of intervention second treated eyes at one year versus 0/9 of control first- or second-treated eyes. After crossover, delayed intervention improvements of logMAR 0.3 seen in 11% (1/9) of first-treated eyes and in 22% (2/9) of second-treated eyes. https://secure.aao.org/aao/meeting-archive **March 2019** Presented at the 14th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD 2019), March 26 – 31, 2019, Lisbon, Portugal. Clinical Development of a Gene Therapy for an Inherited Retinal Degenerative Disease: A Success Story
Session: Pre Conference Symposium: Common Features of Neurodegenerative Diseases: Exploring the Brain-eye Connection and Beyond Chung D, et al. Based on the results presented, GlobalData inferred that a total of 31 subjects were analyzed in this study. All 31 subjects met with statistical significance its primary endpoint including the bilateral mobility test change score (p = 0.001) and the first two of three secondary endpoints including full-field light sensitivity threshold testing, or FST (p < 0.001), and the assigned first eye mobility test

change score (p = 0.001). Statistical significance was not achieved for the visual acuity (p = 0.17).
https://cmoffice.kenes.com/cmsearchableprogrammeV15/conferencemanager/programme/personid/anonymous/adpd19/normal/b833d15f547f3cf698a5e922754684fa334885ed#!abstractdetails/0000227450 **September 20, 2018** European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP)
Public Assessment Report of Luxturna (voretigene neparvovec) Based on the results reported, GlobalData inferred that there is a change in score from baseline to 1 year after exposure to study drug using the company's in-house mobility tool in this study. Bilateral MT Change Score, Year 1 Compared to Baseline

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			

https://www.ema.europa.eu/en/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf **April 2019** Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2019), April 28 - May 02, 2019, Vancouver, British Columbia, Canada Impact of Voretigene Neparvovec on Legal Blindness in Germany in Patients with RPE65 Mutation-Associated Inherited Retinal Dystrophy − Post Hoc Analysis of Phase III Trial Data
Session: Gene therapy for ocular disorders
Abstract No.: 3388 - A0159 Sue Lacey et al. Based on the results presented, GlobalData inferred that a total of 169 subjects were analyzed in the study. Among 29 subjects who receiving voretigene neparvovec in phase III study (original intervention and delayed intervention group), 11 (38%) subjects were considered as legally blind according to German definition. A total of eight (73%) subjects were no longer fulfilled the criteria for the legal blindness one year after receiving treatment. A total of three subjects remained legally blind. The proportion of non-legally blind subjects in phase III trial elevated from 62% at the baseline to 90% at year one and which was maintained up to year three. At one year follow-up of delayed intervention group (pre-intervention), one subject was out of seven turned legally blind according to German definition and subjects who were legally blind at screening, remained as blind (n=2).

Parameter	Blind, number of subjects, n	Non-blind, number of subjects, n
Baseline (N=29)	11	18
Year 1 (N=29)	3	26
Year 2 (N=29)	3	26
Year 3 (N=22)	2	20

https://eventpilot.us/doc/clients/ARVO/ARVO19/library/pdf/abstract_310890.pdf?display (Pages 46-47) **May 01, 2019** Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2019), April 28 - May 2, 2019, Vancouver, British Columbia, Canada Visual Function Questionnaire Responses in the Voretigene Neparvovec Phase 3 Trial
Session: Visual Impairment and Patient Reported Outcomes
Abstract No.: 4968 - A0378 Stephen R Russell et al. Based on the results presented, GlobalData inferred that subjects in both arms were observed with following VFQ changes and comparison of intervention versus control arms at year 1, nominal p for subjects was 0.001 and nominal p for parents was 0.002.

Parameter	Experimental arm	Control arm
Mean VFQ change from baseline at year 1 for subjects	+2.6 (1.8)	+0.1 (1.4)
Mean VFQ change from baseline at year 1 for parents	+3.9 (1.9)	-0.2 (1.3)
Subject with mean VFQ change from baseline at year 1, n	20	09
Parent with mean VFQ change from baseline at year 1, n	15	05

https://eventpilot.us/doc/clients/ARVO/ARVO19/library/pdf/abstract_310985.pdf?display (Page 03) **September 2019**

Presented at the 29th International Congress of the European Respiratory Society (ERS 2019), September 28 – October 02, 2019, Madrid, Spain

Four-year update for the phase 3 voretigene neparvovec-rzyl study in biallelic RPE65 mutation–associated inherited retinal disease
Session: Age-Related Macular Degeneration I

Stephen R Russell et al,

Based on the results presented, GlobalData inferred that the there was no below pre-treatment performance and showed maintained functional MLMT scores in

subjects. There was no deleterious immune response observed in subjects. There was improved ambulatory navigation, VF and light sensitivity which was maintained for at least 4 years after VN administration in OI subjects. There was improved DI subjects which was consistent with those observed in OI subjects.

Findings

Parameter	**Observation**
Change of 1 light level	5
Mean change in white light FST in $\log_{10}$ (cd.s/m2) averaged over both eyes $\log_{10}$ at Year 4 for OI subjects, n	1.90 (1.33) (19)
Mean change in subjects at $\log_{10}$ Year 3 for DI subjects	2.91 (1.05)
Mean change in VA (Holladay Scale) averaged over both eyes (logMAR) for OI subjects	-0.00 (0.75)
Subjects at year 3 for DI subjects	-0.06 (0.24)
Mean change in GVF III4e sum total degrees averaged over both eyes at year 4 for OI subjects, n	197.7 (282.7) (18)
Subjects at year 3 for DI subjects	157.9 (325.3) (8)

https://www.xcdsystem.com/retinasociety/program/5axOY6c/index.cfm?pgid=56
September 2019

Presented at the 19th Congress of The European Society of Retina Specialists (EURETINA 2019), September 05-08, 2019, Palais des Congres, Paris, France Vision-dependent Activities of Daily Living after Ocular Gene Therapy: Visual Function Questionnaire Responses in the Voretigene Neparvovec Phase 3 Trial Session: New Drug Treatment and Technology

Leroy B et al.

Based on the results presented, GlobalData inferred that subject- and parent-completed visual function questionnaire showed significant, durable improvement after voretigene neparvovec treatment.
http://www.euretina.org/congress/paris-2019/paris-2019-abstracts/?type=2&title=New+Drug+Treatment+and+Technology&sessiom=806&type=2 **May 04, 2020** Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2020), May 03 - 07, 2020, Baltimore, Maryland Psychometric evaluation of a modified version of the Visual Function Questionnaire using data from a Phase III trial in biallelic RPE65 mutation-associated inherited retinal dystrophy
Session:Rehabilitation outcomes
Abstract no:1578 - A0291 Judit Banhazi et al. Based on the results presented, GlobalData inferred that 31 subjects were analyzed in the study. Subjects indicated sensitivity to improvements in functional vision following voretigene

	neparvovec treatment, despite skewed item response distributions across timepoints.Correlations among items were weak-to-moderate (0.00–0.66) at baseline and slightly stronger at 1-year (0.00–0.87). Internal consistency was excellent across timepoints (Cronbach's alpha=0.854–0.950) and test-retest reliability was strong between days 90–180 (Intraclass Correlation Coefficient=0.912), indicating excellent reliability. Moderate correlations with similar measures post-BL (r=−0.48 to 0.76) supported convergent validity. Statistically significant differences post-baseline ($p<0.001$) in mean mVFQ-25 scores between groups defined by MLMT scores, supported discriminative validity.Statistically significant changes in mVFQ-25 for patients who had improved MLMT scores supported responsiveness. Distribution and anchor-based analyses to define meaningful change thresholds suggested that a 1.5-point change or more can be considered meaningful. Reliability, validity and responsiveness of mVFQ-25 as a measure of functional vision for use in subjects with IRD due to RPE65 mutations. https://eventpilot.us/web/page.php?page=IntHtml&project=ARVO20&id=3358455 **November 13, 2020** Presented at the 124th Virtual Annual Meeting of the American Academy of Ophthalmology (AAO 2020), November 13 - 15, 2020, Las Vegas, Nevada, USA Phase III Trial Update of Voretigene Neparvovec-rzyl in Biallelic RPE65 Mutation–Associated Inherited Retinal Disease Session: Retina, Vitreous Abstract No.: PO405 Albert M Maguire et al., Based on the results presented, GlobalData inferred that a total of 29 subjects were analyzed in the study. The MLMT mean (SD) bilateral light level change score for OI subjects at Year 5 (n = 18) and DI subjects at Year 4 (n = 8) was 1.6 (1.1) and 2.4 (1.5) levels respectively, compared to baseline. There was an improvement of one light level in six subjects following the 1-year results and no change in the remaining 20 (N = 26). The mean change in FST white light in log10 ($cd.s/m^2$) was -2.02 (1.45) log10 for OI subjects at Year 5 (n = 17) and -2.58 (1.04) log10 for DI subjects at Year 4 (n = 8). https://secure.aao.org/aao/meeting-archive **May 2021** Presented at the Virtual Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2021), May 01 - 07, 2021 Five-year Post-injection Results of the Phase 3 Trial of Voretigene Neparvovec-rzyl in Biallelic Rpe65mutation-associated Inherited Retinal Disease Session: Visual Impairment - Assessment and Measurement Abstract No.: 3546151 Jean Bennett et al. Based on the results presented, GlobalData inferred that for original intervention subjects at year 5 (n=18) and delayed intervention subjects at year 5 (n=7), the multi-luminance mobility test (MLMT) mean (SD) bilateral light level change score was 1.6 levels (1.2) and 2.4 levels (1.6), respectively compared to baseline. The combined (original intervention plus the delayed intervention groups) mean bilateral light level change score was 1.8 (1.3) (N=25). Mean change in white light full field light sensitivity threshold test (FST) in log10 ($cd.s/m^2$) was −2.02 (1.45) log10 at Year 5 for original intervention subjects (n=17) and −2.57 (1.21)

<table>
<tr><td></td><td>log10 at year 5 for delayed intervention subjects (n=7).

The mean change in white light full field light sensitivity threshold test in log10 (cd.s/m^2) was -2.18 (1.38) for the combined original intervention and delayed intervention group (N=24). https://www.arvo.org/globalassets/annual-meeting/arvo-2021/arvo-2021-abstracts.pdf (Page no.3112)
Based on the results reported, visual improvements were maintained for at least five years after voretigene neparvovec-rzyl administration for both the original intervention and delayed intervention subjects
Based on the results reported, AAV2-hRPE65v2 gene therapy (SPK-RPE65) was effective in subjects with Leber Congenital Amaurosis.</td></tr>
<tr><td>Safety Result</td><td>February 10, 2023

Taiwan Food and Drug Administration (TFDA) Assessment Report of Luxturna_concentrate_and_solvent_for_solution_for_injection Based on the results reported, GlobalData inferred that safety analysis was performed in this study. The main safety concerns include increased intraocular pressure,mintraocular infection and/or inflammation, cataract, retinal abnormalities (e.g., retinal tears, retinal detachment, macular holes, foveal thinning, foveal dehiscence), which may occur following vitrectomy and/or subretinal injection. https://www.fda.gov.tw/tc/includes/GetFile.ashx?mid=189&id=42534&t=s

April 15, 2020

Swissmedic Switzerland Swiss Public Assessment Report (SwissPAR) of LUXTURNA (Voretigene)Based on the pooled results of NCT00516477, NCT01208389, NCT00999609 reported, Global data inferred that safety results were analyzed.
<table>
<tr><th colspan="3">Percentage of patients with adverse drug reactions in clinical studies</th></tr>
<tr><th>Frequency group</th><th>ADRs</th><th>Studies 101 + 102 + 301 (N=41 subjects) n (%)</th></tr>
<tr><td colspan="3">Eye disorders</td></tr>
<tr><td rowspan="2">Very common</td><td>Conjunctival hyperaemia</td><td>9 (22)</td></tr>
<tr><td>Cataract</td><td>8 (20)</td></tr>
<tr><td rowspan="6"></td><td>Retinal tear</td><td>4 (10)</td></tr>
<tr><td>Macular hole</td><td>3 (7)</td></tr>
<tr><td>Retinal deposits</td><td>3 (7)</td></tr>
<tr><td>Corneal dellen</td><td>3 (7)</td></tr>
<tr><td>Eye inflammation</td><td>2 (5)</td></tr>
<tr><td>Maculopathy</td><td>2 (5)</td></tr>
</table></td></tr>
</table>

	Eye irritation	2 (5)
	Eye pain	2 (5)
	Retinal detachment	1 (2)
	Retinal haemorrhage	1 (2)
	Choroidal haemorrhage	1 (2)
	Endophthalmitis	1 (2)
	Macular degeneration	1 (2)
	Conjunctival cyst	1 (2)
	Eye disorders	1 (2)
	Eye swelling	1 (2)
	Foreign body sensation in the eyes	1 (2)
	Retinal disorder	1 (2)
Investigations		
Very common	Increased intraocular pressure	6 (15)
Common	Electrocardiogram T wave inversion	1 (2)
Psychiatric disorders		
Common	Anxiety	1 (2)
Nervous system disorders		
Common	Headache	3 (7)
	Dizziness	1 (2)
Gastrointestinal disorders		
Common	Nausea	3 (7)
	Vomiting	2 (5)
	Upper abdominal pain	1 (2)
	Lip pain	1 (2)
Skin and subcutaneous tissue disorders		
Common	Rash	1 (2)
	Swelling of face	1 (2)
Injury, poisoning and procedural complications		
Common	Endotracheal intubation complication	1 (2)
	Wound dehiscence	1 (2)

https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/swisspar/swisspar-luxturna.pdf.download.pdf/2020-04-15_SwissPAR_Luxturna-FINAL.pdf

	October 10, 2015 Spark Therapeutics Announces Presentation of Additional Phase 3 and Durability Data on SPK-RPE65 at The Retina Society 48th Annual Scientific Meeting Based on the results announced by Spark Therapeutics, Inc. in the press release, GlobalData inferred that serious adverse events related to SPK-RPE65 were not reported. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle_print&ID=2095955 **January 11, 2016** Presented at the 34th Annual JP Morgan Healthcare Conference, January 11-14, 2016, California, USA Based on the results presented, GlobalData inferred that drug related serious adverse events were not observed during the study. http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjA2NjY0fENoaWxkSUQ9MzE5MDgwfFR5cGU9MQ==&t=1 (Slides 03, 04, 10, 11, 12, 13, 23). **November 04, 2015** Spark Therapeutics Reports Third Quarter 2015 Financial Results and Recent Business Highlights Based on the results announcd by the Spark Therapeutics, in the press release, GlobalData inferred that SPK-RPE65 was found to be well tolerated. Serious adverse events related to SPK-RPE65 or deleterious immune responses were not observed. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2106466 **August 10, 2016** Spark Therapeutics Announces New Positive Data from Continuation of Phase 3 Trial of Voretigene Neparvovec Based on the results announced by Spark Therapeutics, Inc. in the press release, GlobalData inferred that the safety profile was largely consistent with the prior studies. There were no product candidate related serious adverse events or SAEs reported in this study. There was only one SAE observed in one eye, which was determined to be associated to the surgical procedure rather than the voretigene neparvovec. This subject had shown a decline in visual acuity post-surgical procedure and had not returned to the baseline, however, this subject had shown an improvement on the MT and also exhibited a gain in the FST. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2194535 **August 10, 2016** Spark Therapeutics Reports Second Quarter 2016 Financial Results and Recent Business Highlights Based on the results announced by Spark Therapeutics in the press release, GlobalData inferred that drug related serious adverse events or serious adverse events were not observed during the study but procedure-related adverse event was observed in one subject during the study. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2194546 **September 09, 2016** Presented at the 16th EURETINA Congress 2016, September 8-11, Bella Center, Copenhagen, Denmark Phase 3 efficacy and safety study of voretigene neparvovec (AAV2hRPE65v2) in subjects with RPE65 mediated inherited retinal dystrophy Free Paper Session 18: New Drug Treatment and Technology 1 Leroy B et al. Based on the results presented, GlobalData inferred that serious adverse events were not observed during the study.

http://euretina.org/copenhagen2016/programme/free-papers-details.asp?id=4657&day=0 **November 03, 2016** Spark Therapeutics Reports Third Quarter 2016 Financial Results and Recent Business Highlights Based on the results announced by Spark Therapeutics, in the press release, GlobalData inferred that crossover group safety results were consistant with prior studies. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2219135 **January 10, 2017**

Presented at the 35th Annual J.P. Morgan Healthcare Conference, January 09-11, 2017, San Fransisco, California, USA

Based on the results presented, GlobalData inferred that product related serious adverse events were observed during the study with voretigene. http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjU2NjIwfENoaWxkSUQ9MzYzMjU1fFR5cGU9MQ==&t=1 (Page 08,09,10,12) **February 15, 2017** 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) (AAV2-hRPE65v2-301) Based on the results presented, GlobalData inferred that

Serious adverse events	**Intervention**	**Control**
Total subjects affected by serious adverse events		
Subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)
Nervous system disorders		
Convulsion		
Additional description: Associated with pre-existing complex seizure disorder.		
Subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
Occurrences causally related to treatment / all	0 / 1	0 / 0
General disorders and administration site conditions		
Adverse drug reaction		
Additional description: Associated with pre-existing complex seizure disorder and complications of oral surgery, respectively.		
Subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)
Occurrences causally related to treatment / all	0 / 2	0 / 0
Frequency threshold for reporting non-serious adverse events: 3%		
Non-serious adverse events	**Intervention**	**Control**
Total subjects affected by non serious adverse events		

Subjects affected / exposed	20 / 20 (100.00%)	9 / 9 (100.00%)
Vascular disorders		
Hypertension		
Subjects affected / exposed	1 / 20 (5.00%)	1 / 9 (11.11%)
Occurrences all number	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Oral fibroma		
Subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
Occurrences all number	1	0
Immune system disorders		
Seasonal allergy		
Subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)
Occurrences all number	0	1
General disorders and administration site conditions		
Chest pain		
Subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
Occurrences all number	1	0
Chills		
Subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
Occurrences all number	1	0
Facial pain		
Subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
Occurrences all number	1	0
Fatigue		
Subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
Occurrences all number	1	0
Pain		
Subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
Occurrences all number	1	0
Pyrexia		
subjects affected / exposed	7 / 20 (35.00%)	1 / 9 (11.11%)
occurrences all number	9	2
Psychiatric disorders		
Anxiety		
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)
occurrences all number	0	2

Attention deficit/hyperactivity disorder		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
occurrences all number	1	0
Emetophobia		
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)
occurrences all number	0	1
Insomnia		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
occurrences all number	1	0
Reproductive system and breast disorders		
Dysmenorrhoea		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
occurrences all number	3	0
Menometrorrhagia		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
occurrences all number	1	0
Menstruation irregular		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
occurrences all number	1	0
Injury, poisoning and procedural complications		
Animal bite		
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)
occurrences all number	2	0
Ankle fracture		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
occurrences all number	1	0
Excoriation		
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)
occurrences all number	0	1
Eye injury		
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)
occurrences all number	0	1
Foot fracture		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
occurrences all number	1	0
Joint sprain		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)

occurrences all number	1	0
Laceration		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)
occurrences all number	1	0
Muscle strain		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)

https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002109-20/results **June 2017** Spark Therapeutics Inc. Corporate Presentation Based on the results presented, GlobalData inferred that the product related SAEs were not occured in this study. phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjY1OTEzfENoaWxkSUQ9MzgxMTUwfFR5cGU9MQ==&t=1 (Slides 03,04,07,08,09,10,21) **July 13, 2017**

Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial

Stephen Russell et al.

The Lancet, 2017

Based on the results published, GlobalData inferred that drug-related serious adverse events (SAEs) or deleterious immune responses were not reported.

In an intervention group, two subjects, one with a pre-existing complex seizure disorder and another subject who experienced oral surgery complications, reported SAEs unrelated to trial participation. Most of the ocular events reported were mild in severity. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31868-8/abstract **July 13, 2017**

Spark Therapeutics Announces Publication in The Lancet of Pivotal Phase 3 Clinical Trial Data for Investigational Voretigene Neparvovec

Based on the results announced by Spark Therapeutics, Inc., in the press release, GlobalData inferred that the most frequent ocular adverse events (AEs) reported were transient elevated intraocular pressure, transient mild ocular inflammation, cataracts and intraoperative retinal tears. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2286471 **July 31, 2017** Spark Therapeutics Submits Marketing Authorization Application to European Medicines Agency for Investigational LUXTURNA (voretigene neparvovec) Based on the results reported by Spark Therapeutics, in the press release, GlobalData inferred that one serious adverse event (SAEs) related to the surgical procedure in one eye of a subject reported in

the study was foveal thinning and a sustained reduction in visual acuity (VA). The most common adverse events reported in 10 percentage of subjects or greater were conjunctival hyperemia, cataract, intraocular pressure increased, and retinal tear. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2290110 **September 06, 2017** Spark Therapeutics Inc Corporate presentation Based on the results reported GlobalData inferred that no product related adverse events are found and below are the findings :

Most common treatment-emergent ocular adverse events	**Number of participants(N=29)**
Increased intraocular pressure	5
Cataracts	4
Retinal tear	3
Retinal deposit	4
Macular hole	2
Transient and mild eye inflammation	2
Eye pain	2
Eye pruritus	2
Procedure-related serious adverse event	**Number of participants(N=29)**
Loss of foveal function (visual acuity) – right eye	1

phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9Njc3MDEwfENoaWxkSUQ9Mzg4MTM0fFR5cGU9MQ==&t=1 **October 12, 2017** Spark TherapeuticsSpark Therapeutics (ONCE) Trading of Stock Halted as FDA Advisory Committee Reviews Investigational Gene Therapy Based on the results announced by Spark Therapeutics in the press release, GlobalData inferred that voretigene neparvovec reported two ocular serious adverse events during the study. http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&cat=news&id=2306224 **November 10, 2017** Three-year Follow-up Phase 3 Data Provide Additional Information on Efficacy, Durability and Safety of Investigational LUXTURNA (voretigene neparvovec) in Patients with Biallelic RPE65-mediated Inherited Retinal Disease Based on the results announced by Spark Therapeutics in the press release, GlobalData inferred that no new serious adverse events (SAEs) with LUXTURNA or deleterious immune responses were observed. Most ocular adverse events (AEs) were mild in severity, with the most common being cataract, elevated intraocular pressure, retinal deposits and retinal tears. One subject in the crossover group experienced an SAE related to the surgical procedure in which there was foveal thinning and a sustained reduction in VA. Three subjects in the intervention group had SAEs unrelated to study participation.

http://ir.sparktx.com/news-releases/news-release-details/three-year-follow-phase-3-data-provide-additional-information
March 26, 2018

Safety and Efficacy Study in Subjects With Leber Congenital Amaurosis

Based on the study results reported, GlobalData inferred that a total of 31 subjects were analyzed in the study.

	Intervention	Control
Total, All-Cause Mortality	0/21 (0.00%)	0/10 (0.00%)
Total, Serious Adverse Events	2/20 (10.00%)	0/9 (0.00%)
Nervous system disorders	1/20 (5.00%)	0/9 (0.00%)
Events	1	0
Surgical and medical procedures	2/20 (10.00%)	0/9 (0.00%)
Events	2	0

https://clinicaltrials.gov/ct2/show/results/NCT00999609?sect=X370156 **May 01, 2018** Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2018), Apr 29 - May 03, 2018, Honolulu, Hawaii, USA Three-year update for the phase 3 voretigene neparvovec study in biallelic RPE65 mutation–associated inherited retinal disease
Session: Profound Low Vision and Low-vision Clinical Trials
Abstract No.: 3900 - C0366 Stephen R Russell et al. Based on the results presented, GlobalData inferred that safety profile was consistent with the vitrectomy and subretinal injection procedure, and deleterious immune responses were not occurred.
https://ep70.eventpilot.us/web/page.php?page=IntHtml&project=ARVO18&id=2915552 **September 14, 2018** Presented at the 51st Scientific Meeting of The Retina Society Annual meeting 2018, September 12 - 15, 2018, San Francisco, California Three-year Update for the Phase 3 Voretigene Neparvovec-rzyl Study in Biallelic RPE65 Mutation–Associated Inherited Retinal Disease
Session: Genetics Diseases, Dystrophies and Degenerations Thomas ciulla et al, Based on the results presented, GlobalData inferred that safety profile in subjects was consistent in subjects.
https://www.xcdsystem.com/retinasociety/program/ldA8aA9/index.cfm?pgid=21&SearchTerm= **October 29, 2018** Spark Therapeutics Presents Three Post-hoc Analyses from Phase 3 Clinical Trial of LUXTURNA (voretigene neparvovec-rzyl) at American Academy of Ophthalmology Annual Meeting Based on the results from three post-hoc analyses announced by Spark Therapeutics Inc., in the press release, GlobalData inferred that adverse events associated with a reduction

	in visual acuity were observed across the LUXTURNA clinical development program. In the post-marketing setting, one adverse event of reduced visual acuity was reported within the immediate post-operative period following administration. It was considered non-serious and is reported to be resolving. Adverse events associated with administration were not observed between RPE65 mutation subtype. http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-presents-three-post-hoc-analyses-phase-3 **November 23, 2018** European Commission Approves Spark Therapeutics' LUXTURNA (voretigene neparvovec), a One-time Gene Therapy for Inherited Retinal Disease Caused by Confirmed Biallelic RPE65 Mutations Based on the pooled results of NCT01208389, NCT00516477, NCT00999609 announced by the Spark Therapeutics in the press release, GlobalData inferred that the most common adverse reactions related to voretigene neparvovec included conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain and maculopathy (wrinkling on the surface of the macula) were observed. http://ir.sparktx.com/news-releases/news-release-details/european-commission-approves-spark-therapeutics-luxturnar **March 2019** Presented at the 14th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD 2019), March 26 – 31, 2019, Lisbon, Portugal. Clinical Development of a Gene Therapy for an Inherited Retinal Degenerative Disease: A Success Story Session: Pre Conference Symposium: Common Features of Neurodegenerative Diseases: Exploring the Brain-eye Connection and Beyond Chung D, et al. Based on the results presented, GlobalData inferred that serious side effects include endophthalmitis was reported and may lead to blindness, permanent visual acuity loss or retinal changes causing vision loss. Other potential side effects includes hyperemia, cataracts, Increased intraocular pressure, retina tears, epiretinal membrane, corneal dellen, macular hole, subretinal deposits, conjunctival edema, eye irritation or pain were reported. https://cmoffice.kenes.com/cmsearchableprogrammeV15/conferencemanager/programme/personid/anonymous/adpd19/normal/b833d15f547f3cf698a5e922754684fa334885ed#!abstractdetails/0000227450 **September 20, 2018** European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) Public Assessment Report of Luxturna (voretigene neparvovec) Based on the results reported, GlobalData inferred that a total of 13 (65%) subjects in the Intervention group had at least one TEAE that assessed in this study 301. A total of six Control / Intervention subjects has at least one TEAE that assessed in this study 302. https://www.ema.europa.eu/en/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf **September 2019** Presented at the 29th International Congress of the European Respiratory Society (ERS 2019), September 28 – October 02, 2019, Madrid, Spain Four-year update for the phase 3 voretigene neparvovec-rzyl study in biallelic RPE65 mutation–associated

	inherited retinal disease Session: Age-Related Macular Degeneration I Stephen R Russell et al, Based on the results presented, GlobalData inferred that the the safety profile was consistent with vitrectomy and the subretinal injection procedure in subjects. There was one subject with who had retinal detachment 4 years after treatment. There was consistent safety profile in subjects. https://www.xcdsystem.com/retinasociety/program/5axOY6c/index.cfm?pgid=56
Pharmacokinetic Evaluation	
Statistical Method (if any)	**September 09, 2016** Presented at the 16th EURETINA Congress 2016, September 8-11, Bella Center, Copenhagen, Denmark Phase 3 efficacy and safety study of voretigene neparvovec (AAV2hRPE65v2) in subjects with RPE65 mediated inherited retinal dystrophy Free Paper Session 18: New Drug Treatment and Technology 1 Leroy B et al. Based on the results presented, GlobalData inferred that wilcoxon ranksum test was used to compare outcomes between the intervention and control groups in the study. http://euretina.org/copenhagen2016/programme/free-papers-details.asp?id=4657&day=0
Conclusion	The trial was completed. Based on the results reported, GlobalData concluded that AAV2-hRPE65v2 gene therapy (SPK-RPE65) is effective and safe in improving visual function in subjects with Leber Congenital Amaurosis.

Enrollment Data	
Trial Start Date (Actual):	01 Oct 2012
No. of Subjects Planned:	27
Trial Enrollment Completion Date (Actual):	21 Nov 2013
No. of Subjects Enrolled:	31
Enrollment Period (in Months) (Actual):	13.87

Enrollment Efficiency (%):	31
Trial End Date (Actual):	06 Apr 2015
No. of Sites:	2
Treatment Period (in Months) (Actual):	16.70
Trial Duration (in Months) (Actual):	30.57

Enrollment Rate Parameters:	
Subjects/Site:	15.50
Subjects/Month:	2.24
Subjects/Site/Month:	1.12

Trial Cost Overview	
Trial Cost Parameters	**Cost ($ Millions)**
Trial Cost	38.84
Trial Cost/Month	1.27
Trial Cost/Site	19.42
Trial Cost/Subject	1.25

Trial Cost By Year	
Year	**Trial Cost ($ Millions)**
2012	3.86
2013	15.10
2014	15.10
2015	3.99

Trial Cost By Components	
Cost Components	**Cost ($ Millions)**
Admin Costs	3.88

Central Lab	4.66
Subject Costs	4.27
Personnel Costs	10.10
Site Costs	15.92

Investigators Information			
Name	Albert M Maguire	Role	Principal Investigator
Specialty	Ophthalmology	Board Certification	
Primary Designation	Professor	Associated Organization	University of Pennsylvania
Contact Number	1-215-5902791; 1-800-7897366; 1-215-6628100	Email	amaguire@mail.med.upenn.edu
State	Pennsylvania	Country	United States

Similar studies done by Investigator

Investigators Information			
Name	Stephen R Russell	Role	Principal Investigator
Specialty	Ophthalmology	Board Certification	
Primary Designation	Professor	Associated Organization	University of Iowa
Contact Number	1-319-3564588; 1-319-4672000; 1-800-7778442	Email	steve-russell@uiowa.edu
State	Iowa	Country	United States

Similar studies done by Investigator

Investigators Information			
Name	Katherine A High	Role	Co-Author
Specialty	Hematology; Internal Medicine	Board Certification	
Primary Designation	Director	Associated Organization	Children's Hospital of Philadelphia

Contact Number	1-215-2209336; 1-215-5901000; 1-215-5901710	Email	higj@email.chop.edu
State	Pennsylvania	Country	United States

Similar studies done by Investigator

Investigators Information			
Name	Daniel Chung	Role	Co-Author
Specialty	Radiology	Board Certification	
Primary Designation	Consultant Radiologist	Associated Organization	Cardiff and Vale University Health Board
Contact Number	44-29-20747747	Email	
State	Wales	Country	United Kingdom

Similar studies done by Investigator

Investigators Information			
Name	Lisa M Sullivan	Role	Co-Author
Specialty	Biostatistics; Epidemiology	Board Certification	
Primary Designation	Professor	Associated Organization	Boston University School of Public Health
Contact Number	1-617-3581489; 1-617-3539403	Email	lsull@bu.edu
State	Massachusetts	Country	United States

Location(s) (3)

Region	Country	State	Trial Site	Address	Status
Europe	Germany				Completed
North America	United States	Iowa	University of Iowa	University of Iowa, Iowa City, Iowa, United States, 52242	Completed
North America	United States	Pennsylvania	Children's Hospital	Children's	Completed

			of Philadelphia	Hospital of Philadelphia, Philadelphia, Pennsylvania, United States, 19104	

Investigator Affiliated Site(s)(15)					
Region	**Country**	**State**	**Trial Site**	**Address**	**Status**
North America	United States	Massachusetts	Boston University School of Public Health	Talbot Building, 715 Albany St. Boston, MA 02118	
North America	United States	Pennsylvania	Hospital of the University of Pennsylvania	3400 Spruce Street, Philadelphia, PA, 19104	
North America	United States	Maryland	Johns Hopkins University School of Medicine	Baltimore, Maryland, 21287, United States	
North America	United States	Pennsylvania	Penn Medicine	800 Spruce Street, Philadelphia, PA 19107	
North America	United States	Pennsylvania	Perelman School of Medicine at the University of Pennsylvania	3400 Civic Center Boulevard, Building 421, Philadelphia, PA 19104	
North America	United States	California	University of California San Francisco	Box XXXX 550 16th St., Floor 4, San Francisco, CA 94143	
North America	United States	Iowa	University of Iowa Hospitals and Clinics	200 Hawkins Drive, Iowa City, IA, 52242	

North America	United States	Pennsylvania	University of Pennsylvania	Philadelphia, PA 19104	
North America	United States	New York	NewYork-Presbyterian Hospital	5141 Broadway, New York, NY 10034	
North America	United States	Pennsylvania	Scheie Eye Institute	Penn Presbyterian Medical Center, 51 N. 39th Street, Philadelphia, PA 19104	
Europe	United Kingdom	Wales	Cardiff and Vale University Local Health Board	Heath Park, Cardiff CF14 4XW	
Europe	Belgium	East Flanders	Ghent University	Coupure links 653 9000 Gent Belgium	
Europe	Belgium	East Flanders	Ghent University Hospital	C. Heymanslaan 10 9000 Gent	
Asia-Pacific	Australia	Queensland	University of Queensland	Level 2, Public Health Building, School of Population Health, University of Queensland, Herston Road, Herston, QLD 4006	
Asia-Pacific	Australia	Queensland	Australian Institute for Bioengineering and Nanotechnology	Corner College and Cooper Rds (Bldg 75), The University of Queensland, Brisbane QLD 4072, Australia	

Contact Detail(s)

Contact Person Name	Phone Number	Email ID	Address	State	Country	Region
Albert M Maguire	1-215-8980915, 1-800-7897366	amaguire@mail.med.upenn.edu	Penn Presbyterian Medical Center, Scheie Eye Institute, 51 N 39th Street, Philadelphia, Pennsylvania 19104, United States	Pennsylvania	United States	North America
Steven John Russell	1-617-7268722, 1-617-7261848	sjrussell@partners.org, steven.russell@joslin.harvard.edu	MGH Diabetes Unit, 50 Staniford Street, 3rd Floor, S50-340, Boston, MA 02114	Massachusetts	United States	North America
Kathleen A Marshall	267-426-7875	marshallk1@email.chop.edu	Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States, 19104	Pennsylvania	United States	North America

Site Coordinator Detail(s)

Site Coordinator Name	Email	Phone	Address	Organization	Site Name
Albert M Maguire	amaguire@mail.med.upenn.edu	1-215-8980915, 1-800-7897366	Penn Presbyterian Medical Center, Scheie Eye Institute, 51 N 39th Street, Philadelphia, Pennsylvania 19104, United States	Penn Presbyterian Medical Center	Penn Presbyterian Medical Center, Philadelphia, 19104
Kathleen A Marshall	marshallk1@email.chop.edu	267-426-7875	Children's Hospital of Philadelphia, Philadelphia,	Children's Hospital of Philadelphia	Children's Hospital of Philadelphia, Philadelphia,

			Pennsylvania, United States, 19104		19104
Earlene Slaymaker	earlene-slaymaker@uiowa.edu		University of Iowa,Iowa City, Iowa, United States, 52242	University of Iowa	University of Iowa, Iowa City, 52242

Key Trial Events (67)

Event Date	Event Brief	Event Type	Source
26 Jun 2023	Novartis Receives Approval for Luxturna, First Gene Replacement Therapy in Eye Diseases	Trial Update	https://www.novartis.com/jp-ja/news/media-releases/prkk20230626
03 Sep 2022	Voretigene Neparvovec Exploratory Analysis (VNEAN): R-shiny App for the Comprehensive and Dynamic Visualization of Voretigene Neparvovec Clinical Trial Data Trial results updated	Results	https://euretina.softr.app/abstract?recordId=reco0qS5eixiKHFRi
01 May 2021	Five-year Post-injection Results of the Phase 3 Trial of Voretigene Neparvovec-rzyl in Biallelic Rpe65mutation-associated Inherited Retinal Disease Results updated	Results	https://www.arvo.org/globalassets/annual-meeting/arvo-2021/arvo-2021-abstracts.pdf (Abstract No.: 3546151)
13 Nov 2020	Phase III Trial Update of Voretigene Neparvovec-rzyl in Biallelic RPE65 Mutation–Associated Inherited Retinal Disease Results updated	Results	https://secure.aao.org/aao/meeting-archive
04 May 2020	Psychometric evaluation of a modified version of the Visual Function Questionnaire using data from a Phase III trial in biallelic RPE65 mutation-associated inherited retinal dystrophy Results updated	Results	https://eventpilot.us/web/page.php?page=IntHtml&project=ARVO20&id=3358455
28 Sep 2019	Four-year update for the phase 3 voretigene neparvovec-rzyl study in biallelic RPE65 mutation–associated	Results	https://www.xcdsystem.com/retinasociety/program/5axOY6c/index.cfm?pgid=56

	inherited retinal disease Trial Results updated		
05 Sep 2019	Vision-dependent Activities of Daily Living after Ocular Gene Therapy: Visual Function Questionnaire Responses in the Voretigene Neparvovec Phase 3 Trial Trial results updated	Results	http://www.euretina.org/congress/paris-2019/paris-2019-abstracts/?type=2&title=New+Drug+Treatment+and+Technology&sessiom=806&type=2
04 Sep 2019	UK's NICE recommends Novartis' Luxturna gene therapy for rare eye disease	Trial Update	https://www.novartis.co.uk/news/media-releases/nice-recommends-novartis%27-luxturnav-voretigene-neparvovec-first-one-time-gene,https://www.england.nhs.uk/2019/09/nhs-to-fund-revolutionary-treatment-for-blindness-in-children/,https://in.reuters.com/ar
01 May 2019	Visual Function Questionnaire Responses in the Voretigene Neparvovec Phase 3 Trial Trial results has been updated.	Results	https://eventpilot.us/doc/clients/ARVO/ARVO19/library/pdf/abstract_310985.pdf?display
28 Apr 2019	Impact of Voretigene Neparvovec on Legal Blindness in Germany in Patients with RPE65 Mutation-Associated Inherited Retinal Dystrophy − Post Hoc Analysis of Phase III Trial Data Trial results updated.	Results	https://eventpilot.us/doc/clients/ARVO/ARVO19/library/pdf/abstract_310890.pdf?display (Pages 46-47)
26 Mar 2019	Clinical Development of a Gene Therapy for an Inherited Retinal Degenerative Disease: A Success Story Trial Results updated	Results	https://cmoffice.kenes.com/cmsearchableprogrammeV15/conferencemanager/programme/personid/anonymous/adpd19/normal/b833d15f547f3cf698a5e922754684fa334885ed#!abstractdetails/0000227450
06 Feb 2019	Gene therapy treatment targets rare form of inherited vision loss	Trial Update	https://medicine.umich.edu/dept/ophthalmology/news/archive/201902/gene-therapy-treatment-targets-rare-form-inherited-vision-loss

23 Nov 2018	European Commission approves Spark Therapeutics' LUXTURNA (voretigene neparvovec), a one-time gene therapy for inherited retinal disease caused by confirmed Biallelic RPE65 mutations Trial pooled results updated	Pooled Results	http://ir.sparktx.com/news-releases/news-release-details/european-commission-approves-spark-therapeutics-luxturnar, Children's Hospital Celebrates European Commission Approval of First-of-its-kind Gene Therapy for Blindness
29 Oct 2018	Spark Therapeutics presents three post-hoc analyses from phase 3 clinical trial of LUXTURNA (voretigene neparvovec-rzyl) at American Academy of Ophthalmology Annual Meeting Results updated	Results	http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-presents-three-post-hoc-analyses-phase-3
29 Oct 2018	Visual Acuity Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial Trial results updated	Results	https://secure.aao.org/aao/meeting-archive
28 Oct 2018	RPE65 Mutation Subtype Effects on Baseline Visual Function and Treatment Response in Phase 3 Voretigene Neparvovec Trial Trial results updated.	Results	https://secure.aao.org/aao/meeting-archive
28 Oct 2018	Cone-Mediated Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial Results updated	Results	https://secure.aao.org/aao/meeting-archive
21 Sep 2018	Novartis announces positive CHMP opinion for one-time gene therapy Luxturna to treat children and adults with rare inherited retinal disease	Trial Update	http://www.globenewswire.com/news-release/2018/09/21/1574243/0/en/Novartis-announces-positive-CHMP-opinion-for-one-time-gene-therapy-Luxturna-to-treat-children-and-adults-with-rare-inherited-retinal-disease.html
21 Sep 2018	Year 3 results and agestratified analyses for a phase 3 trial of voretigene neparvovec in RPE65 mutation–associated inherited retinal disease Trial results updated.	Results	http://www.euretina.org/congress/vienna-2018/vienna-2018-abstracts/?title=Free%20Paper%20Session%2011:%20New%20Drug%20Treatment%20&%20Technology%20I&sessiom=733&title=Free%20Pa

			per%20Session%2011:%20New%20Drug%20Treatment%20&%20Technology%20I
17 Sep 2018	Year 1 time to mobility test completion in a voretigene neparvovec trial in subjects with RPE65 mutation–associated inherited retinal disease Results updated	Results	http://www.euretina.org/congress/vienna-2018/vienna-2018-abstracts/?title=Free%20Paper%20Session%2018:%20New%20Drug%20Treatment%20&%20Technology%20II&sessiom=740&title=Free%20Paper%20Session%2018:%20New%20Drug%20Treatment%20&%20Technology%20II
16 May 2018	Assessment of Bilateral Retinal Gene Therapy of the Phase 3 LCA2 Clinical Trial: A Longitudinal fMRI Study of Binocular Visual Functions Results updated	Results	https://plan.core-apps.com/asgct2018/abstract/c3f26eef-44bb-455c-96fc-2561e734e2c7
01 May 2018	Three-year update for the phase 3 voretigene neparvovec study in biallelic RPE65 mutation–associated inherited retinal disease Trial results updated	Results	https://ep70.eventpilot.us/web/page.php?page=IntHtml&project=ARVO18&id=2915552
23 Mar 2018	Clinical trial registry update. Trial results updated.	Results	• https://clinicaltrials.gov/ct2/history/NCT00999609?A=17&B=18&C=Side-by-Side#StudyPageTop
23 Feb 2018	Spark Therapeutics to Participate in Multiple Conferences in March	Trial Update	http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-participate-multiple-conferences-march-0
03 Jan 2018	Spark's Gene Therapy Treatment for Blindness LUXTURNA to Cost $850,000	Trial Update	https://www.sec.gov/Archives/edgar/data/1609351/000119312518001117/d519914d8k.htm
19 Dec 2017	FDA Approves Spark Therapeutics LUXTURNA (voretigene neparvovec-rzyl), a One-time Gene Therapy for Patients with Confirmed Biallelic	Results	http://ir.sparktx.com/news-releases/news-release-details/fda-approves-spark-therapeutics-luxturnatm-

	RPE65 Mutation-associated Retinal Dystrophy Results reported		voretigene-neparvovec
14 Nov 2017	Phase 3 Trial Update of Voretigene Neparvovec in Biallelic RPE65-Mediated Inherited Retinal Disease Results updated	Results	https://secure.aao.org/aao/meeting-archive
10 Nov 2017	Three-year Follow-up Phase 3 Data Provide Additional Information on Efficacy, Durability and Safety of Investigational LUXTURNA (voretigene neparvovec) in Patients with Biallelic RPE65-mediated Inherited Retinal Disease Results updated	Results	http://ir.sparktx.com/news-releases/news-release-details/three-year-follow-phase-3-data-provide-additional-information
10 Nov 2017	Genetic Treatment for Blindness May Soon be Reality	Trial Update	https://www.prnewswire.com/news-releases/genetic-treatment-for-blindness-may-soon-be-reality-300554127.html
02 Nov 2017	Spark Therapeutics to Participate in Multiple Upcoming Conferences	Trial Update	http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-participate-multiple-upcoming-conferences-1
12 Oct 2017	FDA Advisory Committee Unanimously Recommends Approval of Investigational LUXTURNA (voretigene neparvovec) for Patients with Biallelic RPE65-mediated Inherited Retinal Disease	Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2306441
12 Oct 2017	Spark Therapeutics (ONCE) Trading of Stock Halted as FDA Advisory Committee Reviews Investigational Gene Therapy Results reported	Results	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&cat=news&id=2306224
06 Sep 2017	Spark Therapeutics Announces Publication of Study Confirming Novel Tests Validity, Reliability and Ability to Detect Change in Functional Vision	Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2298672
06 Sep 2017	Spark Therapeutics Inc. "Corporate Presentation (Slides 4, 15, 16, 17, 18), 6 Sep 2017 Results updated	Results	phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9Njc3MDEwfENoaWxkSUQ9Mzg4MTM0f

			FR5cGU9MQ==&t=1
02 Aug 2017	Spark Therapeutics Reports Second Quarter 2017 Financial Results and Recent Business Progress	Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle_print&ID=2290972
31 Jul 2017	Spark Therapeutics Submits Marketing Authorization Application to European Medicines Agency for Investigational LUXTURNA (voretigene neparvovec) Trial results updated	Results	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2290110
17 Jul 2017	Spark Therapeutics' Biologics License Application for Investigational Voretigene Neparvovec Accepted for Filing by FDA Trial results updated	Results	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2286691
13 Jul 2017	Spark Therapeutics Announces Publication in The Lancet of Pivotal Phase 3 Clinical Trial Data for Investigational Voretigene Neparvovec Trial results updated	Results	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2286471
13 Jul 2017	Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial Trial results updated	Results	http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31868-8/abstract
01 Jun 2017	Spark Therapeutics, Inc. Corporate Presentation Results updated	Results	phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjY1OTEzfENoaWxkSUQ9MzgxMTUwfFR5cGU9MQ==&t=1 (Slides 03,04,07,08,09,10,21)
18 May 2017	Spark Therapeutics Completes Rolling Biologics License Application Submission to FDA for Investigational Gene Therapy Voretigene	Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2273905
10 May 2017	Year 2 results for a phase 3 trial of voretigene neparvovec in biallelic RPE65 -mediated inherited retinal disease Results updated	Results	http://www.arvo.org/webs/am2017/sectionpdf/PH/Session%20424%20Drug%20and%20gene%20therapy%20and%20delivery.pdf (Page 21)

09 May 2017	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 Results updated	Results	www.arvo.org/webs/am2017/sectionpdf/LV/Session%20344%20Functioning%20with%20Low%20Vision.pdf
06 Mar 2017	The 37th Cowen and Company Annual Health Care Conference Results updated	Results	phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjYyMjg0fENoaWxkSUQ9MzY5NDAzfFR5cGU9MQ==&t=1 (Slides 03,07,08, 09,10,12)
22 Feb 2017	Spark Therapeutics Reports 2016 Financial Results and Business Highlights	Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2248148
10 Jan 2017	The 35th Annual J.P. Morgan Healthcare Conference Results updated	Results	http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjU2NjIwfENoaWxkSUQ9MzYzMjU1fFR5cGU9MQ==&t=1
09 Jan 2017	Spark Therapeutics Announces U.S. Orphan Drug Designation Amendment and Study Updates for Lead Investigational Gene Therapy	Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2234931
03 Nov 2016	Spark Therapeutics Reports Third Quarter 2016 Financial Results and Recent Business Highlights Results updated	Results	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2219135
09 Sep 2016	Phase 3 efficacy and safety study of voretigene neparvovec (AAV2hRPE65v2) in subjects with RPE65 mediated inherited retinal dystrophy Trial result updated	Results	http://euretina.org/copenhagen2016/programme/free-papers-details.asp?id=4657&day=0
10 Aug 2016	Spark Therapeutics Reports Second Quarter 2016 Financial Results and Recent Business Highlights Trial results updated	Results	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2194546
10 Aug 2016	Spark Therapeutics Announces New Positive Data from Continuation of Phase 3 Trial of Voretigene Neparvovec	Results	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2194535

	Result updated		
01 Jul 2016	Spark Therapeutics Announces Publication of Positive Follow-Up Data from Phase 1 Trial of Voretigene Neparvovec in The Lancet	Results;Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2181454
04 May 2016	Spark Therapeutics Reports First Quarter 2016 Financial Results and Recent Business Highlights	Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2164808
04 May 2016	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	Results	Daniel J Hui, "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", The 19th American Society of Gene and Cell Therapy (ASGCT) Annual Meeting, Session: Gene Therapy for Neurosensory Diseases, Abstract no.: 185, 04 May 2016
09 Mar 2016	Spark Therapeutics Reports 2015 Financial Results and Business Highlights	Results;Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2147143
11 Jan 2016	Spark Unveils Vision of Having 10 Clinical-Stage Gene Therapy Programs by 2018, Including One Commercial and Two in Pivotal Trials	Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2128384
14 Nov 2015	Spark Therapeutics Announces Presentation of Additional Phase 3 Data on SPK-RPE65 at The American Academy of Ophthalmology 2015 Annual Meeting	Results;Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2112455
04 Nov 2015	Spark Therapeutics Reports Third Quarter 2015 Financial Results and Recent Business Highlights	Results;Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2106466
10 Oct 2015	Spark Therapeutics Announces Presentation of Additional Phase 3 and	Enrollment Status;Results	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-

	Durability Data on SPK-RPE65 at The Retina Society 48th Annual Scientific Meeting		newsArticle_print&ID=2095955
05 Oct 2015	Foundation Fighting Blindness Applauds Phase 3 Study Results for Investigational Gene Therapy Treatment	Results;Trial Status;Trial Update	http://www.prnewswire.com/news-releases/foundation-fighting-blindness-applauds-phase-3-study-results-for-investigational-gene-therapy-treatment-300153860.html
09 Sep 2015	Spark Therapeutics Announces Database Lock for SPK-RPE65 Phase 3 Clinical Trial and Expected Release of Top-Line Data in October	Trial Update	http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle_print&ID=2086609
18 Mar 2015	Spark Therapeutics Reports Full Year 2014 Financial Results	Trial Update	http://www.sparktx.com/sites/default/files/fields/press-release/spark_therapeutics_2014_earnings_release_3.18.15_web.pdf
06 Nov 2014	Spark Therapeutics Receives FDA Breakthrough Therapy Designation for Its Lead Product Candidate, SPK-RPE65	Trial Update	http://www.sparktx.com/sites/default/files/fields/press-release/breakthrough_therapy_designation_press_release_november_6_2014_final.pdf
16 Sep 2014	Spark Therapeutics Appoints Gene Therapy Pioneer Dr. Katherine A. High as President and Chief Scientific Officer	Trial Update	http://www.sparktx.com/sites/default/files/fields/press-release/kathy_release_102114_finalv3.pdf
13 May 2014	Spark Therapeutics Establishes Permanent Headquarters in West Philadelphia	Trial Update	
14 Jan 2014	Spark Therapeutics Achieves Recruitment Goal in Phase 3 Gene Therapy Clinical Study for Inherited Blindness	Enrollment Status;Trial Status;Trial Update	http://www.sparktx.com/sites/default/files/fields/press-release/jpm-ph_3_announcement.pdf
09 Dec 2013	Spark Therapeutics Co-Founder and Gene Therapy Pioneer Dr. Katherine A. High Outlines Challenges and Promises for Gene Therapy	Trial Update	http://www.sparktx.com/sites/default/files/fields/press-release/ash_press_release.pdf

Insights (9)	
Published Date	**Headline**

15-Feb-2017	Spark’s voretigene triggers optimism on LCA approval but pause on a broader label
11-Nov-2016	Spark’s Phase III signals for voretigene neparvovec sees experts continue to question clinical meaning despite interim success
11-Nov-2016	Spark’s voretigene neparvovec for LCA will see some Phase I/II decline in durability, clinical significance debated - experts
19-Mar-2015	Spark Therapeutics gene therapy for LCA2 has experts optimistic on chances for statistical significance in Phase III
13-Mar-2015	Spark's LCA2 gene therapy is likely to have greater benefit for younger patients - experts
30-Mar-2018	Spark’s Luxturna label including 12-month old patients gives some physicians pause; uptake overall to be strong, with at least three patients treated
30-Mar-2018	Spark’s use of light sensitivity tests for outcomes-based rebates less favorable versus functional measures and task-linked questionnaires, say experts
25-Sep-2018	ProQR’s QR-110 for LCA has strong Phase I/II efficacy despite small dataset; long-term genetic safety, durability still in question, experts say
29-Jan-2021	Approval prospects of GenSight’s Lumevoq in LHON premature based on current Phase III results; experts question natural history data benchmark

History of changes

Modified Date	Update Type	Description	From Data	To Data	Source Date	Source Type	Source
13-Feb-2023	Trial Result	Trial Results Updated			10-Feb-2023	Regulatory Website	https://www.fda.gov.tw/tc/includes/GetFile.ashx?mid=189&id=42534&t=s
05-Sep-2022	Trial Result	Trial Results Updated			03-Sep-2022	Conferences	https://euretina.softr.app/abstract?recordId=reco0qS5eixiKHFRi
12-Aug-2022	Trial Result	Pooled Results Updated			15-Apr-2020	Regulatory Website	https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/swissspar/swissspar-luxturna.pdf.download.pdf/2020-04-15_SwissPAR_Luxturna-FINAL.pdf
12-Jul-2021	Primary/ Secondary	Primary Outcome Measure					https://www.arvo.org/globalassets/annual-meeting/arvo-

	outcomes	Updated					2021/arvo-2021-abstracts.pdf (Abstract No.: 3546151)
12-Jul-2021	Study Design/ Trial Description	Trial Description Updated					https://www.arvo.org/globalassets/annual-meeting/arvo-2021/arvo-2021-abstracts.pdf (Abstract No.: 3546151)
12-Jul-2021	Trial Result	Trial Results Updated					https://www.arvo.org/globalassets/annual-meeting/arvo-2021/arvo-2021-abstracts.pdf (Abstract No.: 3546151)
29-Dec-2020	Primary/ Secondary outcomes	Secondary Outcome Measure Updated					https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Clinical-Review--December-16--2017---LUXTURNA.pdf
29-Dec-2020	Subjects	Exclusion Criteria Updated					https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Clinical-Review--December-16--2017---LUXTURNA.pdf
29-Dec-2020	Trial Result	Trial Results Updated					https://www.ema.europa.eu/en/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf
29-Dec-2020	Trial Result	Trial Results Updated					https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Clinical-Review--December-16--2017---LUXTURNA.pdf
29-Dec-2020	Trial Result	Trial Results Updated					https://www.tga.gov.au/sites/default/files/auspar-voretigene-neparvovec-

							201215-pi.pdf
29-Dec-2020	Trial Result	Trial Results Updated					https://www.tga.gov.au/sites/default/files/auspar-voretigene-neparvovec-201215.pdf
23-Nov-2020	Trial Result	Trial Results Updated					
18-Nov-2020	Trial Result	Trial Results Updated					
15-May-2020	Trial Result	Trial Results Updated					https://eventpilot.us/web/page.php?page=IntHtml&project=ARVO20&id=3358455
17-Oct-2019	Trial Result	Trial Results Updated					http://www.euretina.org/congress/paris-2019/paris-2019-abstracts/?type=2&title=New+Drug+Treatment+and+Technology&sessiom=806&type=2
14-Oct-2019	Trial Result	Trial Results Updated					https://www.xcdsystem.com/retinasociety/program/5axOY6c/index.cfm?pgid=56
15-May-2019	Primary/ Secondary outcomes	Secondary Outcome Measure Updated					https://eventpilot.us/doc/clients/ARVO/ARVO19/library/pdf/abstract_310985.pdf?display
15-May-2019	Trial Result	Trial Results Updated					https://eventpilot.us/doc/clients/ARVO/ARVO19/library/pdf/abstract_310985.pdf?display
14-May-2019	Trial Result	Trial Results Updated					https://eventpilot.us/doc/clients/ARVO/ARVO19/library/pdf/abstract_310890.pdf?display
10-May-2019	Trial Result	Trial Results Updated					https://www.ema.europa.eu/en/documents/assessment-report/luxturna-

							epar-public-assessment-report_en.pdf
09-May-2019	Trial Result	Trial Results Updated					
07-May-2019	Acronym/Secondary ID	Trial Secondary ID Updated					https://www.ema.europa.eu/en/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf
07-May-2019	Study Design/ Trial Description	Trial Description Updated					https://www.ema.europa.eu/en/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf
07-May-2019	Trial Result	Trial Results Updated					https://www.ema.europa.eu/en/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf
18-Apr-2019	Trial Result	Trial Results Updated					https://cmoffice.kenes.com/cmsearchableprogrammeV15/conferencemanager/programme/personid/anonymous/adpd19/normal/b833d15f547f3cf698a5e922754684fa334885ed#!abstractdetails/0000227450
20-Mar-2019	Acronym/Secondary ID	Trial Secondary ID Updated					
26-Nov-2018	Trial Result	Trial Results Updated					http://ir.sparktx.com/news-releases/news-release-details/european-commission-approves-spark-therapeutics-luxturnar
21-Nov-	Trial	Trial					https://secure.aa

2018	Result	Results Updated					o.org/aao/meeting-archive
20-Nov-2018	Trial Result	Trial Results Updated					https://secure.aao.org/aao/meeting-archive
19-Nov-2018	Trial Result	Trial Results Updated					https://secure.aao.org/aao/meeting-archive
01-Nov-2018	Trial Result	Trial Results Updated					http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-presents-three-post-hoc-analyses-phase-3
28-Sep-2018	Trial Result	Trial Results Updated					http://www.euretina.org/congress/vienna-2018/vienna-2018-abstracts/?title=Free%20Paper%20Session%2011:%20New%20Drug%20Treatment%20&%20Technology%20I&sessiom=733&title=Free%20Paper%20Session%2011:%20New%20Drug%20Treatment%20&%20Technology%20I
25-Sep-2018	Trial Date	Trial Actual End Date Changed from **"01 Jul 2015"** to **"06 Apr 2015"**	01 Jul 2015	06 Apr 2015			https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002109-20/results
24-Sep-2018	Trial Date	Trial Actual End Date Changed from **"06 Apr**	06 Apr 2015	01 Jul 2015			https://clinicaltrials.gov/ct2/show/NCT00999609?sfpd_s=06%2F01%2F2009&sfpd_e=04%2F22%2F2010

		2015" to **"01 Jul 2015"**					
24-Sep-2018	Trial Date	Trial Actual Start Date Changed from **"15 Nov 2012"** to **"01 Oct 2012"**	15 Nov 2012	01 Oct 2012			https://clinicaltrials.gov/ct2/show/NCT00999609?sfpd_s=06%2F01%2F2009&sfpd_e=04%2F22%2F2010
24-Sep-2018	Trial Result	Trial Results Updated					http://www.euretina.org/congress/vienna-2018/vienna-2018-abstracts/?title=Free%20Paper%20Session%2018:%20New%20Drug%20Treatment%20&%20Technology%20II&sessiom=740&title=Free%20Paper%20Session%2018:%20New%20Drug%20Treatment%20&%20Technology%20II
21-Sep-2018	Trial Result	Trial Results Updated					https://www.xcdsystem.com/retinasociety/program/ldA8aA9/index.cfm?pgid=21&SearchTerm=
13-Aug-2018	Subjects	Trial Subjects Updated					
18-May-2018	Trial Result	Trial Results Updated					https://plan.core-apps.com/asgct2018/abstract/c3f26eef-44bb-455c-96fc-2561e734e2c7
07-May-2018	Trial Result	Trial Results Updated					
07-May-2018	Trial Result	Trial Results					

		Updated					
04-May-2018	Trial Result	Trial Results Updated					https://ep70.eventpilot.us/web/page.php?page=IntHtml&project=ARVO18&id=2915552
27-Mar-2018	Primary/ Secondary outcomes	Primary Outcome Measure Updated					
27-Mar-2018	Primary/ Secondary outcomes	Secondary Outcome Measure Updated					
27-Mar-2018	Subjects	Inclusion Criteria Updated					
27-Mar-2018	Trial Result	Trial Results Updated					
14-Mar-2018	Study Design/ Trial Description	Trial Description Updated					
27-Dec-2017	Trial Result	Trial Results Updated					http://ir.sparktx.com/news-releases/news-release-details/fda-approves-spark-therapeutics-luxturnatm-voretigene-neparvovec
04-Dec-2017	Trial Result	Trial Results Updated					https://secure.aao.org/aao/meeting-archive
24-Nov-2017	Enrollment	Number of Subjects Planned Changed from "24" to "27"	24	27			

24-Nov-2017	Trial Date	Trial Actual End Date Changed from **"05 Oct 2015"** to **"06 Apr 2015"**	05 Oct 2015	06 Apr 2015			
24-Nov-2017	Trial Date	Trial Actual Start Date Changed from **"01 Oct 2012"** to **"15 Nov 2012"**	01 Oct 2012	15 Nov 2012			
14-Nov-2017	Study Design/ Trial Description	Trial Notes Updated					http://ir.sparktx.com/news-releases/news-release-details/three-year-follow-phase-3-data-provide-additional-information
14-Nov-2017	Trial Result	Trial Results Updated					http://ir.sparktx.com/news-releases/news-release-details/three-year-follow-phase-3-data-provide-additional-information
16-Oct-2017	Trial Result	Trial Results Updated					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&cat=news&id=2306224
11-Sep-2017	Trial Result	Trial Results Updated					
02-Aug-2017	Trial Result	Trial Results Updated					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-

							newsArticle&ID=2290110
19-Jul-2017	Trial Result	Trial Results Updated					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2286691
19-Jul-2017	Study Design/ Trial Description	Trial Description Updated					
14-Jul-2017	Enrollment	Number of Subjects Analyzed Changed from "29" to "31"	29	31			http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2286471
14-Jul-2017	Trial Result	Trial Results Updated					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2286471
14-Jul-2017	Trial Result	Trial Results Updated					http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31868-8/abstract
15-Jun-2017	Trial Result	Trial Results Updated					phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjY1OTEzfENoaWxkSUQ9MzgxMTUwfFR5cGU9MQ==&t=1 (Slides 03,04,07,08,09,10,21)
22-May-2017	Trial Result	Trial Results Updated					www.arvo.org/webs/am2017/sectionpdf/LV/Session%20344%20Functioning%20with%20Low%20Vision.pdf
18-May-2017	Primary/ Secondary outcomes	Secondary Outcome Measure Updated					http://www.arvo.org/webs/am2017/sectionpdf/PH/Session%20424%20Drug%20and%20gene%20therapy%20and%20deliv

							ery.pdf (Page 21)
18-May-2017	Trial Result	Trial Results Updated					http://www.arvo.org/webs/am2017/sectionpdf/PH/Session%20424%20Drug%20and%20gene%20therapy%20and%20delivery.pdf (Page 21)
16-May-2017	Trial Date	Trial Actual Start Date Updated					
16-May-2017	Trial Contacts	Trial Contacts Updated					
20-Mar-2017	Trial Result	Trial Results Updated					phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjYyMjg0fENoaWxkSUQ9MzY5NDAzfFR5cGU9MQ==&t=1 (Slides 03,07,08, 09,10,12)
27-Jan-2017	Trial Result	Trial results updated					http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjU2NjIwfENoaWxkSUQ9MzYzMjU1fFR5cGU9MQ==&t=1
26-Dec-2016	Trial Result	Trial results updated					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2219135
28-Sep-2016	Miscellaneous,Trial Result	Trial result, description updated. Primary, secondary end point added					http://euretina.org/copenhagen2016/programme/free-papers-details.asp?id=4657&day=0
18-Aug-2016	Subjects, Trial Result	Trial results and subjects updated					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2194546

17-Aug-2016	Trial Result	Trial results added					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=RssLanding&cat=news&id=2194535
29-Jul-2016	Indications,Subjects	Subject type updated; Indication updated					https://clinicaltrials.gov/archive/NCT00999609/2016_07_25/changes
25-Jul-2016	Miscellaneous,Trial Result	Description, Trial results added					http://www.jefferies.com/CMSFiles/Jefferies.com/files/Conferences/060716/Presentations/Sparks.pdf, http://ois.net/gene-therapies-move-one-step-closer-to-reality/
23-Jun-2016	Trial Result	Study results updated					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2106466
21-Jun-2016	Trial Result	Result updated					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2147143
15-Jun-2016	Trial Result	Study results updated					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2112455
12-May-2016	Miscellaneous,Trial Result	Trial result; Description updated.					http://www.abstractsonline.com/pp8/#!/4077/presentation/165
01-Mar-2016	Trial Result	Trial result updated					http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjA2NjY0fENoaWxkSUQ9MzE5MDgwfFR5cGU9MQ==&t=1
20-Oct-2015	Enrollment,Trial Result	Trial results updated; Trial					http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle_print

		enrollment updated					&ID=2095955
07-Oct-2015	Trial Date,Trial Result,Trial Status	Trial results added; Trial status changed from Ongoing not recruiting to completed; Trial actual end date updated					http://www.prnewswire.com/news-releases/foundation-fighting-blindness-applauds-phase-3-study-results-for-investigational-gene-therapy-treatment-300153860.html
10-Nov-2014	Supplementation Source,Trial Description	Trial description updated; Supplementation source added					http://www.sparktx.com/sites/default/files/fields/press-release/breakthrough_therapy_designation_press_release_november_6_2014_final.pdf
06-Nov-2014	Trial End Date,Trial Status,Validation Source	Trial status changed to "Ongoing, Not recruiting"; Trial end date changed; Validation source added					
29-Oct-2014	Result source,Validation Source	Updated: Validation source; Supplementation source					
21-May-2014	Study Design,S	Updated: Supplemen					

	upplementation Source	tation source; Study design					
21-May-2014	Supplementation Source,Trial Description	Trial description, Supplementation source updated					http://www.sparktx.com/sites/default/files/fields/press-release/arvo_media_advisory.pdf
23-Apr-2014	Supplementation Source,Trial Description,Trial Status	Trial status changed from Recruiting to Ongoing not recruiting; Description updated					http://www.prnewswire.com/news-releases/spark-therapeutics-achieves-recruitment-goal-in-phase-3-gene-therapy-clinical-study-for-inherited-blindness-240098701.html
16-Jan-2014	Collaborator Name,Sponsor Type,Study Type	Trial collaborator added; Interventional study Type tagged; Trial inclusion criteria Updated; Trial sponsor Updated					
23-Oct-2013	Location - Address,Miscellaneous,Trial Description,Validation	Trial description modified; Subjects type updated; Validation source updtaed;					

	Source	Location details updated					
09-Jul-2013	Miscellaneous	Checked and Validated					
10-Apr-2013	Miscellaneous	Checked and validated					
31-Jan-2013	Miscellaneous	Checked and validated					
31-Oct-2012	Participants Criteria (Exclusion),Participants Criteria (Inclusion),Trial End Date,Trial secondary Id,Trial Start Date,Trial Status	Trial status changed from Not yet recruiting to Recruiting; Trial start date changed; Trial end date changed; SUbject criteria modified					
15-Jun-2012	Trial Start Date	Trial start date changed from March 2012 to August 2012					
02-Feb-2012	No.of Subjects Planned	Changed from 12 to 24					
02-Feb-	Participa	Updated					

2012	nts Criteria (Inclusion)						
02-Feb-2012	Primary Objective	Updated					
02-Feb-2012	Secondary Objective	Updated					
02-Feb-2012	Study Design	Added: Randomized Changed from Single Group Assignment to Parallel Assignment					
02-Feb-2012	Trial Description	Updated					
02-Feb-2012	Trial End Date	Changed to December 2028					
07-Dec-2011	Trial Start Date	Changed to March 2012					

Sources

- WHO, International Clinical Trials Registry Platform (ICTRP) Search Portal
- International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) Search Portal
- Spark Therapeutics Inc., "Spark Unveils Vision of Having 10 Clinical-Stage Gene Therapy Programs by 2018, Including One Commercial and Two in Pivotal Trials", 11 Jan 2016
- Spark Therapeutics Inc., "Spark Therapeutics Reports First Quarter 2016 Financial Results and Recent Business Highlights", 04 May 2016
- U. S. Securities and Exchange Commission (SEC), Spark Therapeutics, Inc., FORM 10-Q, 30

Jun 2016 (Page 15)
- U. S. Securities and Exchange Commission (SEC), Novelion Therapeutics Inc., FORM 10-K, 30 Dec 2016 (Page no. 24)
- Spark Therapeutics, "Spark Therapeutics to Participate in J.P. Morgan Healthcare Conference", 03 Jan 2017
- Spark Therapeutics, "Spark Therapeutics Announces U.S. Orphan Drug Designation Amendment and Study Updates for Lead Investigational Gene Therapy", 09 Jan 2017
- Spark Therapeutics, "Spark Therapeutics Reports 2016 Financial Results and Business Highlights", 22 Feb 2017
- Spark Therapeutics, "Spark Therapeutics Completes Rolling Biologics License Application Submission to FDA for Investigational Gene Therapy Voretigene Neparvovec", 18 May 2017
- U. S. Securities and Exchange Commission (SEC), Spark Therapeutics, Inc., FORM 10-Q, 31 Mar 2017
- Spark Therapeutics Inc. "Corporate Presentation (Slides 3, 8-10), 21 Jul 2017
- NHS Choices Information Portal
- Spark Therapeutics, Inc., "Spark Therapeutics Corporate Presentation (Slide No. 04, 14-21, 24)", 3 Aug 2017
- Spark Therapeutics, "FDA Advisory Committee Unanimously Recommends Approval of Investigational LUXTURNA (voretigene neparvovec) for Patients with Biallelic RPE65-mediated Inherited Retinal Disease", 12 Oct 2017
- Spark Therapeutics, "Spark Therapeutics to Participate in Multiple Upcoming Conferences", 02 Nov 2017
- Spark Therapeutics Inc., "FDA Approves Spark Therapeutics' LUXTURNA™ (voretigene neparvovec-rzyl), a One-time Gene Therapy for Patients with Confirmed Biallelic RPE65 Mutation-associated Retinal Dystrophy", 19 Dec 2017 (Results updated)
- GlobalData Primary Research from Insights
- Stephen R Russell, "Three-year update for the phase 3 voretigene neparvovec study in biallelic RPE65 mutation–associated inherited retinal disease", The Association for Research in Vision and Ophthalmology (ARVO 2018) Annual Meeting, Session: Profound Low Vision and Low-vision Clinical Trials, Abstract No.: 3900 - C0366, 01 May 2018 (Results)
- Mariel A Salkeld, "Assessment of Bilateral Retinal Gene Therapy of the Phase 3 LCA2 Clinical Trial: A Longitudinal fMRI Study of Binocular Visual Functions", The 21st American Society of Gene and Cell Therapy (ASGCT) Annual Meeting, Session: Neurologic Diseases (Including Ophthalmic and Auditory Diseases) I, Abtsract No: 291, 16 May 2018 (Results)
- Spark Therapeutics Inc., "Spark Therapeutics Presents Three Post-hoc Analyses from Phase 3 Clinical Trial of LUXTURNA (voretigene neparvovec-rzyl) at American Academy of Ophthalmology Annual Meeting", 29 Oct 2018 (Results)
- Albert M Maguire, "Visual Acuity Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial", The 2018 Annual Meeting of the American Academy of Ophthalmology (AAO 2018), Session: Retina, Vitreous, Abstract No.: PA074, 29 Oct 2018 (Results)
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), "Luxturna (voretigene neparvovec) – Summary of Product Characteristics", (Page 9)

- PR Newswire, News and Information Distribution Service Providers, " Foundation Fighting

Blindness Applauds Phase 3 Study Results for Investigational Gene Therapy Treatment", 05 Oct 2015

- Spark Therapeutics, Inc., "Spark Therapeutics Announces Presentation of Additional Phase 3 and Durability Data on SPK-RPE65 at The Retina Society 48th Annual Scientific Meeting", 10 Oct 2015
- The 34th Annual JP Morgan Healthcare Conference, "Spark Therapeutics, Inc., Company Update Presentation (Slides 03, 04, 10, 11, 12, 13, 23)", 11 Jan 2016
- Daniel J Hui, "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", The 19th American Society of Gene and Cell Therapy (ASGCT) Annual Meeting, Session: Gene Therapy for Neurosensory Diseases, Abstract no.: 185, 04 May 2016
- Spark Therapeutics, Inc., "Spark Therapeutics Announces Presentation of Additional Phase 3 Data on SPK-RPE65 at The American Academy of Ophthalmology 2015 Annual Meeting", 14 Nov 2015
- Spark Therapeutics, "Spark Therapeutics Reports 2015 Financial Results and Business Highlights", 09 Mar 2016
- Spark Therapeutics, Inc., "Spark Therapeutics Reports Third Quarter 2015 Financial Results and Recent Business Highlights", 04 Nov 2015
- The Jefferies 2016 Global Healthcare Conference, "Spark Therapeutics, Inc. Company Update Presentation (Slides 12,13,14,19)", 10 Jun 2016
- Ophthalmology Innovation Summit News, "Gene Therapies Move One Step Closer to Reality", 09 Oct 2015
- Spark Therapeutics, "Spark Therapeutics Announces New Positive Data from Continuation of Phase 3 Trial of Voretigene Neparvovec", 10 Aug 2016
- Spark Therapeutics,"Spark Therapeutics Reports Second Quarter 2016 Financial Results and Recent Business Highlights", 10 Aug 2016
- Spark Therapeutics, "Spark Therapeutics Reports Third Quarter 2016 Financial Results and Recent Business Highlights", 03 Nov 2016
- The 35th Annual J.P. Morgan Healthcare Conference, "Spark Therapeutics Company Update Presentation (Slides 03,07,08,09,10,12)", 10 Jan 2017
- The 37th Cowen and Company Annual Health Care Conference, "Spark Therapeutics Company Update Presentation (Slides 03,07,08,09,10,12)", 06 Mar 2017
- Stephen R Russell, "Year 2 results for a phase 3 trial of voretigene neparvovec in biallelic RPE65 -mediated inherited retinal disease", The Association for Research in Vision and Ophthalmology's (ARVO) 2017 Annual Meeting, Session 424 Drug and gene therapy and delivery, Program No.: 4122, Poster Board No.: B0122, 10 May 2017
- Daniel C Chung,"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", The Association for Research in Vision and Ophthalmology's (ARVO) 2017 Annual Meeting,Session 344 Functioning with low vision, Program No.:3292,Poster Board Number: B0425, 09 May 2017
- Spark Therapeutics Inc. "Corporate Presentation (Slides 03,04,07,08,09,10,21), Jun 2017
- Stephen Russell, "Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase

3 trial", The Lancet, 13 Jul 2017

- Spark Therapeutics, Inc., "Spark Therapeutics Announces Publication in The Lancet of Pivotal Phase 3 Clinical Trial Data for Investigational Voretigene Neparvovec", 13 Jul 2017
- Spark Therapeutics, "Spark Therapeutics' Biologics License Application for Investigational Voretigene Neparvovec Accepted for Filing by FDA", 17 Jul 2017
- Spark Therapeutics Inc., "Spark Therapeutics Submits Marketing Authorization Application to European Medicines Agency for Investigational LUXTURNA (voretigene neparvovec)", 31 Jul 2017
- Spark Therapeutics Inc. "Corporate Presentation (Slides 4, 15, 16, 17, 18), 6 Sep 2017
- Spark Therapeutics, "Spark TherapeuticsSpark Therapeutics (ONCE) Trading of Stock Halted as FDA Advisory Committee Reviews Investigational Gene Therapy", 12 Oct 2017
- Spark Therapeutics, "Three-year Follow-up Phase 3 Data Provide Additional Information on Efficacy, Durability and Safety of Investigational LUXTURNA (voretigene neparvovec) in Patients with Biallelic RPE65-mediated Inherited Retinal Disease", 10 Nov 2017
- Stephen R Russell, "Four-year update for t

- Spark Therapeutics, "Spark Therapeutics Achieves Recruitment Goal in Phase 3 Gene Therapy Clinical Study for Inherited Blindness", 14 Jan 2014 (Trial status; Description)
- Spark Therapeutics, Inc., Company website (In the Clinic) (Outcomes, Study design)
- Spark Therapeutics, "Spark Therapeutics Scientific Advisor to Deliver Keynote at the Association for Research in Vision and Ophthalmology's 2014 Annual Meeting", 08 May 2014 (Description)
- Spark Therapeutics, "Spark Therapeutics Receives FDA Breakthrough Therapy Designation for Its Lead Product Candidate, SPK-RPE65", 06 Nov 2014 (Description)
- Vidyullatha Vasireddy, "AAV-Mediated Gene Therapy for Choroideremia: Preclinical Studies in Personalized Models", PLOS One, 07 May 2013
- VIVO, University of Pennsylvania, Clinical Trials Information Portal
- Spark Therapeutics, "Spark Therapeutics Appoints Rare Disease Pioneer Dr. Rogério Vivaldi a s Chief Commercial Officer ", 16 Dec 2014
- Spark Therapeutics, "Spark Therapeutics Appoints Gene Therapy Pioneer Dr. Katherine A. High as President and Chief Scientific Officer", 16 Jan 2015
- Cowen and Company 35th Annual Healthcare Conference, "Spark Therapeutics, Company Update Presentation (Slides 03, 06, 15)", 04 Mar 2015
- Spark Therapeutics, "Corporate Presentation (Slide: 03, 06, 15)", 04 Mar 2015
- Spark Therapeutics, "Spark Therapeutics to Participate in the 35th Annual Cowen and Company Health Care Conference", 26 Feb 2015
- Spark Therapeutics., "Spark Therapeutics Reports Full Year 2014 Financial Results", 18 Mar 2015
- GlobeNewswire, Corporate News Providers, "Spark Therapeutics to Have Multiple Presentations at 2015 ARVO Meeting", 01 May 2015
- Spark Therapeutics, "Spark Therapeutics Reports Second Quarter 2015 Results", 05 Aug 2015
- Spark Therapeutics, Inc., "Spark Therapeutics Announces Database Lock for SPK-RPE65 Phase 3 Clinical Trial and Expected Release of Top-Line Data in October", 09 Sep 2015 (Trial

description)

- U. S. Securities and Exchange Commission (SEC), Spark Therapeutics, Inc., FORM 10-K, 31 Dec 2015 (Pages 06, 12, 14, 17, 18)
- U. S. Securities and Exchange Commission (SEC), Spark Therapeutics, Inc., FORM 10-Q, 31 Mar 2016 (Pages 14, 25)
- Jean Bennett, "Ocular gene therapy: Clinical successes and lessons learned", 2016 Annual Meeting of the Association for Research in Vision and Ophtalmology (ARVO), Session:165 Gene therapy to rescue vision: From bench to bedside, Program No. 1336, 01 May 2016
- Spark Therapeutics, Inc., "Spark Therapeutics Announces Publication of Positive Follow-Up Data from Phase 1 Trial of Voretigene Neparvovec in The Lancet", 01 Jul 2016
- Spark Therapeutics, Inc., "Spark Therapeutics Corporate Presentation", (Slide 12,13,14,19)Jun 2016
- Leroy B, "Phase 3 efficacy and safety study of voretigene neparvovec (AAV2hRPE65v2) in subjects with RPE65 mediated inherited retinal dystrophy", 16th EURETINA Congress, Free Paper Session 18: New Drug Treatment and Technology 1, 09 Sep 2016 (Result)
- European Union Clinical Trials Registry (EUDRACT) (Sec. ID and contact details)
- U. S. Securities and Exchange Commission (SEC), Spark Therapeutics Inc., FORM 10-Q, 30 Sep 2016 (Page No. 15)
- Spark Therapeutics Inc., "Corporate Overview (Slide No. 03, 06, 08, 19)", 07 Nov 2016
- U. S. Securities and Exchange Commission (SEC), Spark Therapeutics Inc, FORM 10-Q, 31 Dec 2016 (Page No: 6, 8, 12, 15, 16, 18, 44, 81)
- U. S. Securities and Exchange Commission (SEC), Spark Therapeutics Inc, FORM 10-Q, 30 Jun 2017 (Page No: 13, 25-27)
- Spark Therapeutics Inc., "Spark Therapeutics reports second quarter 2017 financial results and recent business progress", 02 Aug 2017
- Spark Therapeutics, "Spark Therapeutics Announces Publication of Study Confirming Novel Test's Validity, Reliability and Ability to Detect Change in Functional Vision", 06 Sep 2017
- Spark Therapeutics Inc. "Corporate Presentation (Slide No. 5-12, 23), 07 Nov 2017 (Trial notes)
- U. S. Securities and Exchange Commission (SEC), Spark Therapeutics Inc, FORM 10-Q, 30 Sep 2017 (Page No. 28)
- Spark Therapeutics, "Three-year Follow-up Phase 3 Data Provide Additional Information on Efficacy, Durability and Safety of Investigational LUXTURNA (voretigene neparvovec) in Patients with Biallelic RPE65-mediated Inherited Retinal Disease", 10 Nov 2017 (trial notes)
- PR Newswire, News and Information Distribution Service Providers, "Genetic Treatment for Blindness May Soon be Reality", 10 Nov 2017
- United states Securities and Exchange Commission (SEC), "Spark Therapeutics, Inc. FORM 8-K", 03 Jan 2018
- Spark Therapeutics, "Spark Therapeutics to Participate in Multiple Conferences in March", 23 Feb 2018
- Thomas ciulla, "Three-year Update for the Phase 3 Voretigene Neparvovec-rzyl Study in Biallelic RPE65 Mutation–Associated Inherited Retinal Disease", The 51st Scientific Meeting of The Retina Society Annual meeting 2018, Session: Genetics Diseases, Dystrophies and Degenerations, 14 Sep 2018(Results)
- GlobeNewswire, Corporate News Providers, "Novartis Announces Positive CHMP Opinion

for One-time Gene Therapy Luxturna to Treat Children and Adults with Rare Inherited Retinal Disease", 21 Sep 2018

- LeRoy B, "Year 1 time to mobility test completion in a voretigene neparvovec trial in subjects with RPE65 mutation–associated inherited retinal diseasey", The 18th Congress of The European Society of Retina Specialists (EURETINA 2018), Session: Free Paper Session 18: New Drug Treatment & Technology II, 22 Sep 2018
- LeRoy B, "Year 3 results and agestratified analyses for a phase 3 trial of voretigene neparvovec in RPE65 mutation–associated inherited retinal disease", The 18th Congress of The European Society of Retina Specialists (EURETINA 2018), Session: Free Paper Session 11: New Drug Treatment & Technology I, 21 Sep 2018 (Results)
- Vinit Mahajan, "RPE65 Mutation Subtype Effects on Baseline Visual Function and Treatment Response in Phase 3 Voretigene Neparvovec Trial", The American Academy of Ophthalmology (AAO) Annual Meeting 2018, Session: Retina, Vitreous, Abstract No.: PO220, 28 Oct 2018 (Results)
- Julia A Haller, "Cone-Mediated Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial", The 2018 Annual Meeting of the American Academy of Ophthalmology (AAO 2018), Session: Retina, Vitreous, Abstract No.: PO225, 28 Oct 2018 (Results)
- University of Michigan, "Gene Therapy Treatment Targets Rare Form of Inherited Vision Loss", 06 Feb 2019
- Genetic Modification Clinical Research Information System (GemCRIS) (pi,sec id)
- Sue Lacey, “Impact of Voretigene Neparvovec on Legal Blindness in Germany in Patients with RPE65 Mutation-Associated Inherited Retinal Dystrophy − Post Hoc Analysis of Phase III Trial Data”, The Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2019), Session: Gene therapy for ocular disorders, Abstract No.: 3388 - A0159, 28 Apr– 02 May 2019
- Stephen R Russell, “Four-year update for the phase 3 voretigene neparvovec-rzyl study in biallelic RPE65 mutation–associated inherited retinal disease”, The 29th International Congress of the European Respiratory Society (ERS 2019), Session: Age-Related Macular Degeneration I, Sep 2019 -(Trial Results)
- Novartis UK, "NICE recommends Novartis’ Luxturna (voretigene neparvovec), the first one-time gene therapy for people with vision loss due to RPE65 genetic mutations", 04 Sep 2019
- Leroy B, “Vision-dependent Activities of Daily Living after Ocular Gene Therapy: Visual Function Questionnaire Responses in the Voretigene Neparvovec Phase 3 Trial”, The 19th Congress of The European Society of Retina Specialists (EURETINA 2019), Session: New Drug Treatment and Technology, Sep 2019 (Results)
- Judit Banhazi, "Psychometric evaluation of a modified version of the Visual Function Questionnaire using data from a Phase III trial in biallelic RPE65 mutation-associated inherited retinal dystrophy", the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2020), Session: Rehabilitation outcomes, Abstract No.: 1578 - A0291, 04 May 2020 (Results)
- Albert M Maguir, “Phase III Trial Update of Voretigene Neparvovec-rzyl in Biallelic RPE65 Mutation–Associated Inherited Retinal Disease”, The 124th Virtual Annual Meeting of the American Academy of Ophthalmology (AAO 2020), Session: Retina, Vitreous, Abstract No.: PO405, 13 Nov 2020 (Results)
- Therapeutic Goods Administration (TGA), "Australian Public Assessment Report (AusPAR)

for Voretigene neparvovec (Luxturna)", 15 Dec 2020 (Page No 13, 14-22, 27)
- Therapeutic Goods Administration (TGA), " Voretigene neparvovec (Luxturna)- Product Information", 15 Dec 2020 (Page No13-20)
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), “Public Assessment Report of Luxturna (Voretigene neparvovec)", 29 Jul 2020 (Page No 25-42)
- U. S. Food and Drug Administration (FDA) – Center for Drug Evaluation and Research (CDER), "Luxturna (Voretigene neparvovec) – Clinical Review", 16 Dec 2017 (Page 39-69)
- GlobalData Primary Research from Insights
- Jean Bennett, “Five-year Post-injection Results of the Phase 3 Trial of Voretigene Neparvovec-rzyl in Biallelic Rpe65mutation-associated Inherited Retinal Disease”, The Virtual Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2021), Session: Visual Impairment - Assessment and Measurement, Abstract No.: 3546151, 01-07 May 2021 (Results)
- Swissmedic Switzerland, "LUXTURNA (Voretigene) - Swiss Public Assessment Report (SwissPAR), 15 April 2020 (Results)
Taiwan Food and Drug Administration (TFDA),"
Luxturna_concentrate_and_solvent_for_solution_for_injection ", 10 Feb 2023 (pg no 5,6) (Result)
- Novartis Pharma K.K., "Novartis Receives Approval for Luxtana, First Gene Replacement Therapy in Eye Diseases", 26 Jun 2023

- U.S. National Institutes of Health Clinical Trials Registry (ClinicalTrials.gov)
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), “Public Assessment Report (EPAR) of Luxturna (voretigene neparvovec)", 20 Sep 2018 (Pages 24, 65, 67, 85) (Results)
- Stephen R. Russell, “Visual Function Questionnaire Responses in the Voretigene Neparvovec Phase 3 Trial”, The Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2019), Session: Visual Impairment and Patient Reported Outcomes, Abstract No.: 4968 - A0378, 01 May 2019 (Results)

Last Reviewed on 13 Feb 2023