20 September 2018
EMA/CHMP/700911/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Luxturna

International non-proprietary name: voretigene neparvovec

Procedure No. EMEA/H/C/004451/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
AAV	Adeno-associated viral
AAV2-hRPE65v2	AAV serotype 2 carrying the human RPE65 cDNA; voretigene neparvovec
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
ANOVA	Analysis of variance
BGH	Bovine growth hormone
BL	Injection baseline
BLA	Biologics License Application
CβA	Chicken beta actin
CCMT	Center for Cellular and Molecular Therapeutics
cDNA	Complimentary deoxyribonucleic acid
CHOP	Children's Hospital of Philadelphia
CI	Confidence interval
CMV	Cytomegalovirus
CS	Contrast sensitivity
CSR	Clinical study report
dB	Decibels
DNA	Deoxyribonucleic acid
DOM	Date of Manufacture
eCTD	Electronic common technical document
EMA	European Medicines Agency
EORD	Early-onset retinal dystrophy
EU	European Union
FDA	Food and Drug Administration
FST	Full-field light sensitivity threshold
GVF	Goldmann visual fields
hRPE	Human retinal pigment epithelium
hRPE65	Human retinal pigment epithelium 65 kDa protein
IND	Investigational new drug
IOP	Intraocular pressure
IRD	Inherited retinal disease
ITR	Inverted terminal repeat
ITT	Intent to treat
kDa	Kilodalton
kg	Kilogram
LCA	Leber congenital amaurosis
LCA2	Leber congenital amaurosis type 2 (due to *RPE65* mutations)
LHON	Leber Hereditary Optic Neuropathy
log10(cd.s/m^2)	Logarithm of candela second per meter squared
LogMAR	Logarithm of the minimum angle of resolution

Abbreviation	Definition
lux	SI unit of illumination; one lumen per square meter
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
mL	Milliliter
mM	Millimolar
MLMT	Multi-luminance mobility testing
MT	Mobility testing
MTVS	Mobility testing validation study
NHx	Natural History
NIH	National Institutes of Health
OCT	Optical coherence tomography
O&M	Orientation and Mobility
polyA	Polyadenylation
PLR	Pupillary light reflex
PP	Per protocol
PPWS	Percentage of preferred walking speed
PT	Preferred term
PWI	Productive walking index
qPCR	Quantitative polymerase chain reaction
RP	Retinitis pigmentosa
RP20	Retinitis pigmentosa type 20 (due to *RPE65* mutations)
RPE	Retinal pigment epithelium
RPE65	Retinal pigment epithelium 65 kDa protein
RPE65	Retinal pigment epithelium 65 kDa protein gene
SAE	Serious adverse event
SECORD	Severe early childhood onset retinal dystrophy
SD	Standard deviation
SE	Standard error
SFU	Spot-forming units
SOC	System organ class
TEAE	Treatment-emergent adverse events
µL	Microliters
µM	Micron
U.S.	United States
VA	Visual acuity
VF	Visual fields
vg	Vector genomes

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Spark Therapeutics Ireland Ltd submitted on 29 July 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Luxturna, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 April 2016.

Luxturna was designated as an orphan medicinal product on 02 April 2012 in the following condition 'treatment of Leber's congenital amaurosis' (EU/3/12/981), and on 28 July 2015 in the following condition 'treatment of retinitis pigmentosa' (EU/3/15/1518).

The applicant applied for the following indication:

Luxturna is indicated for the treatment of patients with vision loss due to Leber's congenital amaurosis or retinitis pigmentosa inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The applicant indicated that voretigene neparvovec was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0221/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application the PIP P/0221/2015 was completed.

The PDCO issued an opinion on compliance for the PIP P/0221/2015.

Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Luxturna as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports. (https://www.ema.europa.eu/en/medicines/human/EPAR/luxturna)

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a

condition related to the proposed indication.

New active Substance status

The applicant requested the active substance voretigene neparvovec contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received Protocol Assistance from the CHMP on:

Scientific advice / Protocol assistance	**date**	**Area**
EMEA/H/SA/2552/1/2013/PA/ADT/PED/SME/ADT/III	25 July 2013	pertained to quality, non-clinical, clinical aspects
EMEA/H/SA/2552/1/FU/1/2015/PA/ADT/III	17 December 2015	pertained to quality, non-clinical, clinical aspects

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

CAT Rapporteur: Christiane Niederlaender CAT Co-Rapporteur: Sol Ruiz

CHMP Coordinator: Nithyanandan Nagercoil CHMP Coordinator: Concepcion Prieto Yerro

PRAC Rapporteur: Brigitte Keller-Stanislawski

The application was received by the EMA on	29 July 2017
The procedure started on	17 August 2017
The CAT agreed to consult the national competent authorities on the environmental risk assessment of the GMO as the ATMP is a gene therapy medicinal product. The consultation procedure started on	7 November 2018
The Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	03 November 2017
The Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	15 November 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	17 November 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2017
The CAT agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	08 December 2017
The applicant submitted the responses to the CAT consolidated List of Questions on	29 March 2018
The following GMP and GCP inspections were requested by the CHMP	

and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at two Investigator sites along with the Sponsor located in USA between December 2017 and January 2018. The outcome of the inspection carried out was issued on	16 Mar 2018
– A GMP inspection at Spark Therapeutics, Philadelphia, PA 19104, USA, site responsible for manufacturing of the active substance and QC testing, between 16 -20 April 2018. The outcome of the inspection carried out was issued on	05/07/2018
– A GMP inspection at PPD Development, Middleton, WI 53562, USA, site responsible for QC testing, on 13 April 2018. The outcome of the inspection carried out was issued on	31/05/2018
– A GMP inspection at Absorption Systems, Exton, PA 19104, USA, site responsible for QC testing, on 19 April 2018. The outcome of the inspection carried out was issued on	08/06/2018
– A GMP inspection at Intertek, Whitehouse, NJ 08888, USA, site responsible for QC testing, on 18 April 2018. The outcome of the inspection carried out was issued on	04/06/2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CAT and CHMP members on	02 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CAT agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	25 May 2018
The applicant submitted the responses to the CAT List of Outstanding Issues on	26 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	6 July 2018
An Ad Hoc Expert Group was convened to address questions raised by the CAT on The CAT and CHMP considered the views of the Expert group as presented in the minutes of this meeting (appendix 1).	5 July 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CAT during the meeting on	18 July 2018
The CAT agreed on a second list of outstanding issues to be addressed in writing to be sent to the applicant on	18 July 2018
The consultation procedure related to the evaluation of the environmental risk assessment of the GMO closed on	20 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the second List of Outstanding Issues to all CAT and CHMP	29 August 2018

members on	
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Luxturna on	14 September 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Luxturna on	20 September 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Leber's congenital amaurosis type 2 and Retinitis pigmentosa are diagnosed in patients with photoreceptor degeneration and who retain central vision within the first decade of life yet with subsequent progression of the disease resulting in profound vision loss during the teenage years. Associated with both clinical diagnoses, there is a reduced or non-detectable electroretinogram as well as attenuated retinal blood vessels and varying amounts of pigmentary deposits within the retina in later stages of the disease process.

It is now considered that the term 'inherited retinal dystrophy due to biallelic RPE 65 mutations' includes / covers all the patients who were previously identified by more than 20-25 different names including Leber's congenital amaurosis and retinitis pigmentosa. It is considered that this is 'genetic definition of a condition' which covers certain (RPE 65 mutation) sub-groups of 'different phenotypic conditions (previously used in the literature)'.

2.1.2. Epidemiology

Leber's congenital amaurosis is estimated to affect about 1 in 80,000 individuals in the EU. 19 different genes have been identified as causing Leber's congenital amaurosis, about 10% cases are caused by a defect in the RPE65 gene (Leber's congenital amaurosis type 2).

Retinitis pigmentosa is estimated to affect about 1 in 4,000 individuals. It is estimated that up to 3% of all patients with Retinitis pigmentosa have underlying genetic mutations in the RPE65 gene.

At present, pathogenic variants in 17 genes have been identified as causing Leber's congenital amaurosis and account for about half of all cases of Leber's congenital amaurosis. Leber's congenital amaurosis type 2 is inherited in an autosomal recessive pattern.

2.1.3. Biologic features

Visual perception results from the biological conversion of light energy to electrical signalling by retinal photoreceptors in the eye. The biochemistry involves consumption and regeneration of 11-cis-retinal, a derivative of vitamin A. One of the enzymes involved in regeneration of 11-cis-retinal is all-trans-retinyl isomerase also known as the retinal pigment epithelium 65 kDa protein [RPE65] encoded by the

RPE65 gene. Subjects are unable to regenerate intra-ocular 11-cis-retinal leading to a profound impairment in the detection of light.

Genetic testing has led to a re-evaluation of how patients are diagnosed. Most subjects with bi-allelic RPE65 mutations carry a diagnosis of Leber's congenital amaurosis type 2. A retrospective clinical case review conducted by the applicant (Study NHx), however, has shown that patients with underlying RPE65 mutations may also be diagnosed as: severe early childhood onset retinal dystrophy (SECORD), tapetal retinal dystrophy-LCA type, delayed retinal maturation and Leber Hereditary Optic Neuropathy.

2.1.4. Clinical presentation and diagnosis

Symptoms of Leber's congenital amaurosis type 2 become evident from 2 – 3 months of age. There is progressive, profound reduction of visual acuity, concentric reduction of visual fields, night blindness and nystagmus. Subjects have great difficulty performing activities of daily living, even under normal daytime lighting conditions. Subjects will be blind by young adulthood.

Retinitis pigmentosa has a more variable onset and slower progression; symptoms usually begin from age 10 years; subjects tend to have better preservation of visual function compared to those with a clinical diagnosis of Leber's congenital amaurosis type 2.

Whilst each subject may express their own age of onset and rate of progression of vision loss, the underlying cause remains the same i.e. biochemical blockade of the visual cycle resulting from RPE65 enzyme deficiency.

2.1.5. Management

There is not a licenced medicinal product for these conditions. Treatment is generally supportive; affected individuals benefit from correction of refractive error and use of low-vision aids.

Surgical devices are available for some subjects who meet clinical requirements: either the Argus® II Retinal Prosthesis System or the Alpha AMS Retina Implant AG. The devices have variable and limited clinical efficacy. Consequently, there is an unmet clinical need for these conditions.

About the product

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

The parent adeno-associated serotype 2 virus, used as a template for the vector, is a non-pathogenic, single-stranded DNA genome-containing, helper virus-dependent member of the parvovirus family

Expression of the gene product of hRPE65, all-trans-retinyl isomerase, in subjects with Leber's congenital amaurosis and who are recipients of Luxturna, will permit these subjects to regenerate intra-ocular 11-cis-retinal and so lead to improvement in the ability to detect light.

Luxturna is presented in cartons containing 1 vial of concentrate and 2 vials of solvent and is for single use only. The product is intended to be applied by an experienced surgeon to the sub-retinal space of each eye.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as concentrate and solvent for solution for injection containing 5 x 10^{12} vector genomes/ml of voretigene neparvovec as active substance.

Voretigene neparvovec is a gene transfer vector that employs an adeno-associated viral vector serotype 2 (AAV2) capsid as a delivery vehicle for the human retinal pigment epithelium 65 kDa protein (hRPE65) cDNA to the retina. Voretigene neparvovec is derived from naturally occurring AAV using recombinant DNA techniques.

Other ingredients are sodium chloride, sodium phosphate and poloxamer 188 for the concentrate and sodium chloride, sodium phosphate, poloxamer 188 and water for injections for the solvent.

The concentrate is available as 0.5 ml extractable volume of concentrate in a 2 ml cyclic olefin polymer vial with a chlorobutyl rubber stopper sealed in place with an aluminium flip-off seal.

The solvent is available as 1.7 ml extractable volume of solvent in a 2 ml cyclic olefin polymer vial with a chlorobutyl rubber stopper sealed in place with an aluminium flip-off seal.

Each foil pouch includes a carton containing 1 vial of concentrate and 2 vials of solvent.

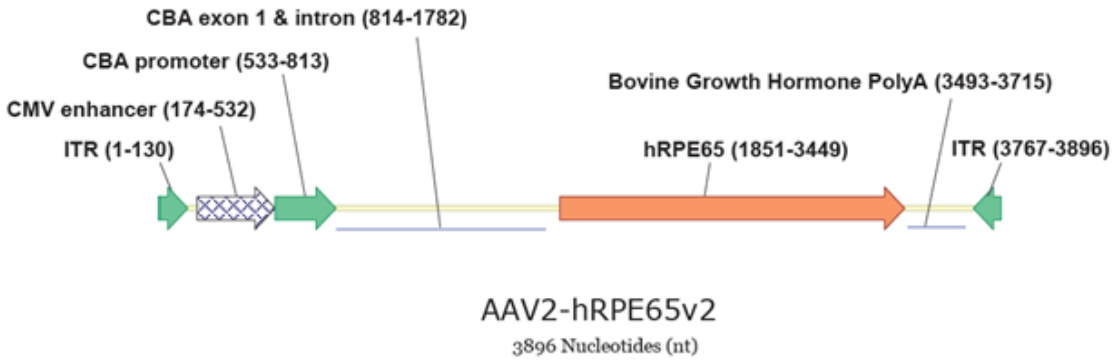
2.2.2. Active Substance

General information

Voretigene neparvovec (AAV2-hRPE65v2) is derived from the naturally-occurring adeno-associated virus serotype 2 (AAV2), which is ubiquitous in the environment and has not been associated with human disease. It is naturally replication deficient, requiring co-infection with helper viruses to replicate. The wild-type virus consists of a single-stranded DNA genome encapsidated in a protein coat. The genome consists of three elements: the rep gene, the cap gene, and the inverted terminal repeats (ITRs). The rep gene codes for proteins involved in DNA replication, and the cap gene, which, through a differential splicing mechanism, encodes three amino-terminal variant virus proteins, VP1, VP2 and VP3, that make up the coat of the virus.

For the recombinant vector voretigene neparvovec, the AAV2 wild-type genome, containing rep and cap genes, is replaced with a therapeutic transgene expression cassette. Short regions of the wild-type AAV DNA containing the ITRs, required for packaging of the therapeutic genome into capsid particles during vector production and for expression of the therapeutic gene in vivo, are retained. The voretigene neparvovec active substance capsid is composed of a total of sixty viral capsid proteins, VP1, VP2, and VP3, that are present at a ratio of approximately 1:1:8, respectively, and assembled into a well-defined icosahedral structure; and one single-stranded DNA molecule containing the therapeutic gene expression cassette, i.e., the vector genome flanked by AAV ITRs. The vector genome diagram for voretigene neparvovec is given in Figure 1 below.

Figure 1 Vector genome diagram for voretigene neparvovec



The voretigene neparvovec (AAV2-hRPE65v2) active substance is a clear, colourless solution at a concentration of 5 x 10^{12} vector genome-containing vector particles per millilitre in water for injection containing sodium chloride, sodium phosphate, Kolliphor P188.

Manufacture, characterisation and process controls

The manufacture of voretigene neparvovec takes place at Spark Therapeutics, Philadelphia, PA 19104, USA. The site has been inspected by the MHRA Inspectorate and is covered by a GMP certificate.

Description of the manufacturing process and process controls

The manufacture of voretigene neparvovec starts with one vial of the Master Cell Bank (MCB), which is used to produce one active substance lot. Cells are expanded, propagated, transfected and purified.

The purified active substance is filled into the final container closure system, which are non-pyrogenic, noncytotoxic, sterile and meets test requirements for USP Class VI plastics.

The description of the manufacturing process and controls is generally adequate, with input parameters and process controls set out. Resin re-use and column sanitation procedures are given as well as process hold times.

No re-processing or re-working has been applied for and is therefore not allowed.

Control of materials

The Starting Materials for manufacture of voretigene neparvovec active substance consist of a mammalian cell substrate and three purified recombinant DNA plasmids. AAV2 is produced in cells through transient transfection with three plasmids that contain the genetic information to produce the coded viral vector.

Master cell bank

The development and characterisation of the MCB and the three purified recombinant DNA plasmids has been adequately described. Screening for a range of specific human, bovine and porcine viruses is performed in accordance with ICH Q5D. The product is currently manufactured directly from vials of the MCB, which has been accepted. The applicant plans to implement a Working Cell bank (WCB), which is currently being qualified, by post-approval variation.

A description of the derivation, characterisation and manufacture of these plasmids has been provided. Tests and specifications for the three plasmids consist of manufacturer's specifications for testing of new lots of plasmid and additional controls performed after receipt for confirmation of new lots of

plasmid prior to release. All plasmids must pass manufacturer's specifications and internal testing criteria to be released by Quality Assurance for use in manufacture. The proposed tests and specifications for all three plasmids are considered adequate.

Excipients and raw materials

Sufficient information on excipients and raw materials used in the active substance manufacturing process has been submitted. All excipients are compendial.

The only material of animal origin used in the current manufacturing process is foetal calf serum, which is supported by a certificate of suitability. The specifications for raw materials used in the manufacturing process are described.

Porcine trypsin has been historically used but has been replaced with a recombinant enzyme for the commercial manufacture.

Control of critical steps and intermediates and process validation

An overview of critical in-process controls and tests performed throughout the voretigene neparvovec active substance manufacturing process is provided.

The control strategy was considered overall insufficient to maintain a consistent process, and a tighter control was requested The applicant has now applied a tightened control, as requested. They are also advised that certain changes to the final approved control strategy as a result of ongoing validation activities should be applied for through a post-authorisation variation procedure.

Validation

The Process Performance Qualification (PPQ) was conducted and the process was demonstrated to operate consistently throughout the PPQ run.

Process validation includes holding steps, cleaning for the CEX resin and TFF#1 membrane and shipping procedures and extractables and leachables, which has been adequately confirmed.

Manufacturing process development

The formulation of the active substance (i.e. sodium phosphate, sodium chloride, and Kolliphor P188) was defined based on pre-formulation and formulation studies conducted to elucidate the solution stability properties of the vector. The pH, buffer type and concentration of the active substance composition provided optimal chemical and physical stability. The finished product solution composition was designed to be the same as the active substance solution composition to enable a simple manufacturing process without requiring dilution of the active substance to produce the final product.

Characterisation

The voretigene neparvovec active substance has been sufficiently characterised by physicochemical and biological state-of-the art methods revealing that the active substance has the expected structure. Some recommendations have been made for the implementation of further characterisation methods to be developed and implemented, post-approval. Process-related impurities are all controlled at batch release. Representative results are provided and conform to pre-determined batch release specifications.

Specification

The specification tests and acceptance criteria for voretigene neparvovec active substance are provided.

Acceptance criteria for active substance have been set on a tolerance interval approach using historical manufacturing data.

Analytical methods

The descriptions of analytical procedures have been provided in adequate detail.

Batch analysis

Batch release data have been presented and all results conform to pre-determined specifications.

Reference material

Voretigene neparvovec have been produced and qualified for use as reference standards for release and stability testing of active substance and finished product. The reference standards are intended for use in multiple analytical procedures. The reference standard will be used as an assay control in release and stability assays. Primary Reference Standard Lot is filled into 2 ml sterile Crystal Zenith vials and stored at ≤ - 65 °C.

To qualify new reference standards, the in-house reference standards (Primary Reference Standard, Working Reference Standard and Interim Reference Standard) have the same formulation as both the active substance and finished product. Each in-house reference standard is qualified using tests and criteria based on the release specifications. The Primary Reference Standard is tested alongside the new reference standard as part of the qualification and a qualification testing protocol has been provided.

Stability

A shelf life at -80 °C is proposed for the active substance.

Comparability Exercise for Active Substance

A comparability evaluation was performed to demonstrate that the active substance produced at Spark is comparable to the material used in the Phase III pivotal clinical study and that the change of manufacturing facility had no impact on the quality attributes of the active substance.

The voretigene neparvovec manufacturing process and unit operations employed at Spark Therapeutics to produce commercial active substance is stated to be the same as the manufacturing process used to produce active substance during clinical development. The evaluation consisted of a combination of analytical release testing and side-by-side testing. A 1:1 comparison was employed. Spark Process Performance Qualification (PPQ) was compared to AAV2-hRPE65v2 clinical lot.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Luxturna finished product is a solution for injection of 5 x 10^{12} vector genomes per mL (0.05 mg vector/ml).

The finished product is formulated as a concentrate and a solvent. Ingredients for the concentrate are sodium chloride, sodium phosphate and poloxamer 188. Ingredients for the solvent are sodium chloride, sodium phosphate, poloxamer 188 and water for injections

It is supplied at a volume of 0.5 ml in a 2 ml Crystal Zenith vial (cyclic olefin polymer) with a chlorobutyl rubber stopper sealed in place with an aluminium flip-off sea. The product requires a 1:10 dilution with diluent prior to administration. There are no novel excipients used in the manufacture of the finished product. All excipients are compendial.

The composition of the finished product is considered acceptable.

Pharmaceutical development

The formulation of the FP has remained unchanged from preclinical supporting studies to phase I/II and III clinical material and commercial product. The proposed commercial product will comprise active substance manufactured at Spark,

Process controls are appropriately defined. Additional data from engineering and PPQ lots indicate that FP and poloxamer 188 levels are maintained during the filtration step of the commercial manufacturing process.

Manufacture of the product and process controls

For manufacture of Luxturna FP, active substance (Bulk Vector) formulated at Spark Therapeutics is shipped frozen to filling site where it is processed into FP by filtration and filling into the final container, Crystal Zenith vials. There is no change in formulation or dilution from active substance to finished product.

The Diluent is manufactured at the Nova Laboratories Ltd facility, Leicester, UK secondary packaging and labelling takes place at Catalent UK Packaging Limited, Lancaster Way, Wingates Industrial Estate, Westhoughton, UK.

The manufacturing process has been validated and adequately described. It has been demonstrated that the manufacturing process is capable of producing finished product of intended quality in a reproducible manner. The in-process controls and ranges defined are adequate.

Process validation consisted of a Process Performance Qualification (PPQ) protocol performed at manufacturing scale, release testing as well as supporting studies including filter validation and media fills.

Reprocessing and/or reworking are not permitted as part of the finished product manufacturing process.

Active substance is shipped to filling site on dry-ice to maintain a target temperature of ≤ -65 ºC. The shipping container is qualified and validated

During commercial distributions, finished product is shipped (at ≤ -65 °C) from the filling site to the secondary packaging and labelling site (Catalent UK Packaging Limited) in insulated shipping

containers (ISC) of semi-finished vials (vials with primary labels applied). The finished product shipping validation has been adequately carried out and data provided in the dossier.

Product specification

The specification tests and acceptance criteria for Luxturna finished product are provided.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

The analytical procedures required for release and stability analysis are summarised

Biological activity is measured with an in vitro potency of enzyme assay. The assay is based on the quantitation of (hRPE65 transgene functional activity) of FP in human cells that contain a plasmid encoding. The purpose of this assay is to determine potency of the gene expression product, RPE65.

The purpose of this assay is to determine potency of the gene expression product, RPE65.

Batch analysis

The PPQ met release specifications.

Reference material

The same reference standard as described under active substance applies.

Stability of the product

The shelf life of Luxturna finished product concentrate and solvent (unopened frozen vials) is 21 months frozen at ≤-65^{o}C.

The applicant has provided device compatibility studies which include in use stability. Good in use stability at 2-8^{o}C and room temperature (after dilution and in the vial/syringe before loading into the device) and further in the administration canula was demonstrated. The proposed in use shelf life of 4 hours is therefore supported.

Comparability exercise for finished product

A comparability evaluation was performed between the PPQ lot and the clinical lot. The evaluation consisted of a combination of analytical release testing and side-by-side testing. A majority of the comparability assessment was performed at the active substance level (see comparability for active substance for further detail). This is considered acceptable for those attributes not expected to change by processing into FP, which consists essentially of transport of the frozen active substance to the filling site, thaw and filling.

Adventitious agents

The Applicant has given a satisfactory overview of the adventitious agent control strategy together with an overview of all materials of human or animal origin. Control of all raw and starting materials has been demonstrated to be satisfactory.

Apart from New Zealand-sourced foetal bovine serum (FBS) used during the cell seeding and cell transfection steps, no other reagents of human or animal origin are used during manufacture. For viral safety, the production cell line has been tested for freedom from adventitious agents. Appropriate measures are taken to ensure safety with respect to bacteria, mycoplasma and TSE.

GMO

Voretigene neparvovec is a disabled recombinant adeno-associated virus serotype 2 (rAAV2) vector that contains an expression cassette for the human retinal pigment epithelium-specific 65 kDa protein (RPE65) gene.

Voretigene neparvovec is a genetically modified organism (GMO) constructed using recombinant DNA technology from wild-type (wt) AAV virus serotype 2 (AAV2), which is a non-pathogenic, single-stranded DNA genome-containing, helper virus-dependent member of the parvovirus family.

Safety features of the virus are described above and an environmental risk assessment in accordance with Directive 2001/18/EC has been presented with respect to the risk of release of GMO into the environment. This assessment is discussed in more detail in the non-clinical part.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality package submitted for voretigene neparvovec (AAV2-hRPE65v2) was missing a substantial amount of information/data. Some of the missing data relates to commercialisation at a relatively early stage of product development. During the procedure the missing information/data has been provided by the applicant. Some information and data remains outstanding, and the CAT/CHMP has agreed that these data can be provided by the applicant as soon as they become available during the post-authorisation phase (see recommendations 1-10).

From the data provided, it is concluded that the manufacturing process is capable of producing a consistent product of acceptable quality. Comparability of the proposed commercial FP with the clinically qualified material was of concern, and underpinned a large number of the issues raised. Tightening of acceptance criteria for critical process controls and release specifications in line with clinically qualified material was considered necessary unless additional validation data could justify the wider ranges claimed. The control strategy has now been tightened in several areas, as requested, and additional validation datasets have been provided. Assays which were insufficiently described have now been more thoroughly detailed and important issues regarding the validation of several critical analytical methods are now largely resolved (see also “Recommendations for future quality development”).

One major objection was initially raised with regard to the site of finished product release testing. In line with the EU legislation, the finished product must undergo in a Member State a full qualitative analysis, quantitative analysis of the active substance and all other necessary quality tests to certify compliance with the requirements of the marketing authorisation. The current FP release testing sites for several quality attributes (including identity, purity and potency) are located in the US. It is noted that the mutual recognition agreement (MRA) for GMP between the US and UK does not apply to ATMPs. However, the recently published Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (Eudralex The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice) allow some flexibility for release testing of ATMPs. The applicant has now justified the proposed release test arrangements. It is accepted that additional testing upon importation into the EU is not required since the FP is manufactured in the EU, and since the small batch size of this orphan product makes dual testing in the EU and US impractical

on the basis that a disproportionate amount of each batch would be used up on batch release/importation testing. Therefore, the current testing plan has been accepted and the major objection was considered resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of Luxturna has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The CAT has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:

None.

The CHMP endorses the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT recommends the following points for investigation: 10 recommendations aimed at providing further data on viral testing, effect of cell passage on CQAs, monitor performance of transfection solutions, ability to adequately discriminate between empty and full capsids, additional characterisation and release test, refine analytical methods and re-valuation of specification once additional batch data becomes available.

The CHMP endorses the CAT assessment regarding the recommendation(s) for future quality development as described above.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant conducted comprehensive battery of tests to characterise non-clinical pharmacology and toxicology of Luxturna.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The applicant presented information from experiments in mice, dogs and monkeys in which treatment with diverse AAVs encoding for RPE65 led to detectable RPE65 protein, where there was none before, restoration of the biochemical pathway in which RPE65 acts, improvement in electroretinograms and in pupillary responses to light stimuli and in behavioural testing, dogs were better ability to navigate an obstacle course after treatment, implying better vision.

In vitro testing in primary normal RPE cells and the same cell population from RPE65-/- dogs (Briard dogs) evaluated expression of RPE65 from AAV2-RPE65 vectors. Briard dogs have a naturally occurring mutation (four base-pair deletion) in canine RPE65 that results in absence of RPE65 protein expression and these dogs have been subject to study over decades and, more recently, used for evaluating RPE65 gene transfer (Veske 1999; Narfstrom 1989). Untreated, they show loss of vision and are considered to be a large animal model of human disease. Transduction of Briard RPE cells with AAV2-RPE65 resulted in expression of the RPE65 transgene, with no evidence of cellular toxicity.

Additional *in vitro* studies were conducted using the virus intended for clinical use (ie voretigene neparvovec, also called AAV2-hRPE65v2). Transduction of normal or mutant Briard RPE cells, using various multiplicities of infection (MOIs), resulted in dose-dependent expression of both hRPE65 mRNA and protein, again with no evidence of cellular toxicity.

An *in vitro* study was performed to compare the levels of RPE65 expressed in cells following transduction with AAV2-hRPE65v1, an earlier version of this virus which lacked certain structural features present in voretigene neparvovec, or following transduction with voretigene neparvovec. Cells were transduced with three different MOIs (1x10e4, 5x10e4, 1x10e5 vg/cell) of either AAV2-hRPE65v1 or voretigene neparvovec. No detectable hRPE65 protein was observed following transduction of cells with AAV2-hRPE65v1 at all three MOIs. In contrast, AAV2-hRPE65v2 resulted in dose-dependent RPE65 expression in cells as assessed by both immunoblot and flow cytometric analyses. These data show that voretigene neparvovec could result in expression of human RPE65 protein in cells and was more effective than the earlier version of the virus. However, it is an unusual finding that AAV2-hRPE65v1 was not active in this testing as this virus was found able to cause the effects to reconstitute RPE65 signalling described above. Differential limitations in sensitivity of different assays could contribute to this profile.

Several *in vivo* studies were done in RPE65-/- mice or Briard (RPE65-/-) dogs. In these, animals were dosed under general anaesthesia with, unlike in human patients, no prophylactic use of steroids to manage inflammation. In some of the early studies in dogs, the virus used encoded for canine RPE65 and not human RPE65; however, latterly, virus encoding human RPE65 (hRPE65) was also used in mice and dogs. In further studies, RPE65-/- mice were also treated.

In testing with the virus intended to be used in the clinic, ie voretigene neparvovec, there were improvement in measures of visual function (which for obvious reasons are more difficult to assess objectively in animals than in humans), and recovery in objective measures (eg electroretinographic responses) with detection of human RPE65 in RPE cells, with no expression in non-RPE cells. Clearly, reconstitution with human protein is able to deliver functional benefit even in REP65-/- dogs and mice.

In these studies, animals used were typically young, reflecting the age of onset of disease in humans in the early years of life. The applicant argued that a dog aged 1.5-5 months (the age of most dogs used) is approximately equivalent in developmental age to a human aged 2-12 years and that for Briard dogs, 1 year is equivalent to 10-15 human years. Testing in older animals has not been done and there is no systematic evaluation of whether efficacy might be lost in older animals. However, the applicant stated that the magnitude of a treatment effect is predicted to be greatest early in life, although, age per se is less important than evaluation of the stage of disease in the retina at the time of treatment.

Regarding the duration of effect, RPE cells are expected to be postmitotic and the virus is not expected to be diluted through cell division, as might occur in other tissues. Systematic study of the duration of response has not been undertaken, but anecdotal evidence from surviving animals indicates long term benefit.

Repeated dosing is intended in humans, that is, one injection into each eye: the possibility that immune responses might result in negation of benefit of the second dose was studied in toxicity studies in the context of assessing the impact of immunogenic responses.

Safety pharmacology programme

Separate safety pharmacology studies were not conducted and are not deemed to be necessary.

2.3.3. Pharmacokinetics

Distribution studies were included as a component of general toxicity studies. Viral shedding was not studied in animals. The transgene encoded by voretigene neparvovec is considered identical to normal human RPE65 protein and so is expected to be metabolised in the same manner as normal human RPE65 protein.

2.3.4. Toxicology

Toxicity was studied in Briard (RPE65-/-) dogs and in animals with normal RPE65 status (dogs, monkeys). In these studies, virus was injected subretinally either once only, or once into each eye, and twice into the same eye. These dosing strategies support the intended human dosing posology of one dose into each eye, ~12 days apart. Animals were followed up after dosing for variable periods but the maximum period was ~7 months. The dose used in general toxicity studies in animals exceeded the dose to be used in humans.

Voretigene neparvovec caused little toxicity with the main issue being inflammatory responses at the injection site. Toxicity identified was minimal and behaviour of the dosed animal was not affected by the described inflammatory injections. It is the applicant's view that, as the dose was higher in animals, these reactions are not likely to be a safety concern in humans. In addition, there was evidence of trauma related to the injection procedure itself.

There are no separate studies investigating reproductive toxicity, genotoxicity, carcinogenicity and local tolerance. However, local tolerance was addressed adequately by the general toxicity studies conducted in dogs and monkeys.

2.3.5. Ecotoxicity / environmental risk assessment

The evaluation of Environmental Risk Assessment was conducted in consultation with national bodies responsible for release of genetically modified organisms into the environment. The main topics were: batch sequencing; the p5 promoter position and potential for minimising homologous recombination between vector plasmid and packaging plasmid; and proof of absence of an ability to transform bacteria and possibly confer resistance to bacteria in the environment. In brief, for the point on batch sequencing, the product will be tested for its identity on import into the EU, and will be tested for gene product expression and potency testing; this was considered sufficient such that sequencing of each bath is not necessary. For the role of the p5 promoter in respect of how the Rep proteins are expressed, the applicant provided additional information, including supporting literature which suggests that reduced rep expression results in higher rAAV yields. The promoter function of p5 is retained, but the modification to p5 reduces this; experimental evidence suggested that the modification of the p5 resulted in reduced rcAAV formation. Finally, the applicant's presented experimental results that were considered sufficient to support the claim that voretigene neparvovec does not have the ability to transform bacteria with kanamycin-resistance.

It has been concluded that Luxturna does not pose a risk to the environment.

2.3.6. Discussion on the non-clinical aspects

The applicant presented sufficient proof of concept to support use of voretigene neparvovec in patients and no further studies in animals are required. The applicant was asked to comment on the level of protein expression required for activity and consider this in the context of relative tropism of voretigene neparvovec for RPE cells from humans, as well as that for cells from mouse, dogs and monkeys and show how these considerations support the dose selected for use in human patients.

The applicant noted that relative transduction efficiency of AAV2 in RPE cells across species is not known but that, given the sizes of eye in dog and mouse, the studies in Briard dogs are more relevant to human effects than those in mice; data on 11-cis-retinal regeneration in such dogs suggests 100% reconstitution of normal RPE65. Minimum levels of hRPE5 reconstitution required to achieve a therapeutic effect in human patients are also not known. The absolute quantity of RPE65 protein in the human eye is not known, but in wild type mice this varies by more than 10-fold from ~0.5-6.5 pg/cell, suggesting that a broad range of RPE65 protein/cell is both well-tolerated and sufficient for visual activity. Because the pharmacology data indicated that efficacy could be achieved over a broad dose range, the determination of the optimal therapeutic dose also relied on safety data. Data from monkeys showed good tolerability at a dose of 5-fold higher (7.5x1011 vg/eye) than the proposed therapeutic dose of 1.5x1011 vg/eye; however, some adverse effects were seen using 1x1012 vg AAV2-hRPE65v1/eye in normal dogs.

There was no toxicity outside the eye and related ocular tissues apart from perivascular lymphocyte cuffing in the brainstem and midbrain. The applicant claimed that this may be a result of immune response to the vector. The applicant was requested to comment further on this and in so doing, indicated that a possible cause is leakage of the vector by reflux into the vitreous chamber that may lead to exposure to the ganglion cells to the vector, leading of transport of both vector and transgene to regions of the brain of the dogs. Since in dogs and primates, presence in the brain of vector sequences was not reported, vector leakage was considered to be limited. Additionally, in humans, measures taken to use a lower dose and use a fluid-air exchange to remove the fluid following intravitreal injection, removing potentially vector leakage, are expected to limit the potential effects of leakage and its consequences.

In respect of biodistribution, the applicant's view was that following subretinal injection there is no systemic exposure to AAV2 and hRPE65 is not expressed except in tissue that is both exposed to virus and has the necessary components to make RPE65 protein. This is supported by the lack of expression of hRPE65 protein when injected into the vitreous and the lack of ability to identify voretigene neparvovec virus in systemic tissues. However, as assays used to detect virus and immune response to the capsid and the transgene were not validated to an acceptable standard, these data are not considered to be definitive.

Voretigene neparvovec delivers human protein to animals and also, unlike in humans, wild-type AAV2 does not naturally infect animals; these elements suggest that immunogenic responses might occur in animals; toxicity evaluations suggested influx to the dosing area of inflammatory cell types assays. When RPE65-/- animals were injected, there was no safety issue identified from immunogenic reactions. Further, the effect of a second injection on transgene expression on activity to improve visual function was not compromised by an immune response to the earlier dose. In normal animals, voretigene neparvovec did not lead to antibody responses against pre-existing RPE65 protein. If there is concern that, in humans, immune responses to injection of voretigene neparvovec could lead to compromise of that degree of hRPE65 function that was remaining prior at the time of injection, there

was no evidence to support this from the preclinical testing conducted. hRPE65 is not expressed in the cell membrane and is located intracellularly and so elimination of transduced cells based on cell-membrane expression of hRPE65 is not an anticipated risk. However, T cell responses were observed to the AAV capsid.

In respect of long term safety, systematic data in long term follow up of animals given voretigene neparvovec were not provided. There is anecdotal information of no concerns identified from a small number of dogs given voretigene neparvovec. However, long term follow up in studies in the literature with rAAV vectors have not identified specific concerns over years of follow up, covering most of the dosed animals' lifespans.

The key findings of relevance to the RMP suggested from the preclinical safety studies are of inflammatory reactions, either to AAV2 capsid or to hRPE65 protein, and risks associated with the intervention associated with dosing voretigene neparvovec, such as infection and accidental trauma.

The patient population to be treated might reasonably be expected to live for decades after dosing and be of an age where they will have children after being treated with voretigene neparvovec. In respect of the risk posed to reproductive health, the applicant's position, that studies are not needed with voretigene neparvovec, rests on two sources of evidence. 1) is that there is no dissemination of voretigene neparvovec to the gonads in either dogs or monkeys and 2) is by reference to published literature. Literature suggests that AAV2 (and other rAAV subtypes) can be detected in the semen of animals dosed systemically, but virus does not persist, being cleared within a few days: vector sequences are not detected in spermatocytes. The risk is reduced comparing this information derived from intravenous dosing, with subretinal dosing, as intended with voretigene neparvovec. The applicant acknowledged that there are fewer data on risk of germline transmission in females. The applicant concluded that reproductive toxicity studies with voretigene neparvovec are not needed.

The CHMP previously gave scientific advice that such studies would not be needed if 'biodistribution data in two species and two sexes demonstrate lack of vector distribution to the gonads'. The applicant considers its dataset to be in line with this advice from CHMP.

Although no distribution in the gonads was reported, two animals showed positive signals in the aqueous fluid of the uninjected eye and no signal in the aqueous fluid of the injected eye. There was also a description that PCR reported no signal in ovaries, whereas the two dogs concerned were males; a similar error occurred in the description of biodistribution data from primates. Ultimately, no explanation for these errors was identified, but gonadal tissues from 18 animals (dogs and primates) were examined with no positive results, which is reassuring.

Concerning genotoxicity, this was addressed in the two scientific advice procedures with CHMP, in 2013 and 2015. The position at the conclusion of these was that the applicant need provide no experimental data with voretigene neparvovec and that a discussion could suffice, if judged adequate. It is acknowledged that there may be some integration events but these are expected to be at random sites: the risk is greatest where the concentration of virus is greatest ie in the retinal pigment epithelial cells. This tissue is understood to be post-mitotic in patients that could be given voretigene neparvovec. AAV integration requires the cells to be dividing and as a consequence, the risk of insertional mutagenesis seems limited: it would not be further understood by requiring experimental work with voretigene neparvovec. CHMP also advised that in vivo testing in 2-year carcinogenicity studies in mice or rats would not contribute meaningful data to assessing the risk of carcinogenicity.

The CHMP endorses the CAT discussion on the non-clinical aspects as described above.

2.3.7. Conclusion on the non-clinical aspects

The data on expression of RPE65 in the retina of injected animals and functional consequences of this (biochemistry, electroretinography, pupillometry and behaviour) are sufficient. An acceptable evaluation of toxicity has been presented and all points raised were resolved. The non-clinical data support a decision in favour of granting a marketing authorisation for this application.

The CHMP endorses the CAT conclusions on the non-clinical aspects as described above.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme has consisted of one phase I study, one phase II study, one phase III study, a natural history study and a study to validate the mobility testing tool developed by the company.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Conventional pharmacokinetic characterisation of the product is not possible and not expected from gene therapy products. Given that AAV2-hRPE65v2 is a gene therapy vector administered via subretinal injection and that systemic exposure is considered to be minimal, it is acceptable. In this regard, the main information regarding vector delivery into the target tissue, persistence of expression and the presence of the functional protein is based on nonclinical studies and vector shedding results from clinical studies. Pharmacokinetic investigation has been limited to a description of elimination of study drug. In clinical studies AAV2-hRPEv2 vector was detected in tears in 17/31 patients (8 subjects treated in Phase 3 study and 9 subjects treated in Phase 1 studies) and peripheral blood samples in 9/31 patients. AAV2-hRPEv2 vector shedding into either tears or peripheral blood appeared to be transient in nature, with the majority of positive samples occurring between one and three days after vector administration. During this three day window, vector shedding tended to be localized to tear samples from the injected eye.

2.4.3. Pharmacodynamics

Mechanism of action

Patients with Leber congenital amaurosis or with retinitis pigmentosa develop progressive sight loss, starting early in life (eg a few years of age) progressing to total blindness. This can arise from mutations in the RPE65 gene which encodes for a protein known as RPE65, which is a 65 kilodalton protein specific for the retinal pigment epithelium. Voretigene neparvovec is a gene therapy based on adeno-associated virus (AAV) serotype 2 into which the human RPE65 gene has been inserted. After

subretinal injection, the product is intended to deliver expression of normal RPE65 protein to reconstitute function of the retinoid cycle, critical in converting incident photons into interpretable electrical signals, and restore vision.

In normal health, RPE65 in retinal pigment epithelial cells converts all-trans-retinol to 11-cis-retinol, which subsequently forms the chomophore, 11-cis-retinal, during the visual (retinoid) cycle, steps critical in conversion of a photon of light into an electrical signal within the retina. RPE65 gene mutations lead to reduced or absent levels of RPE65, blocking this signalling, leading to loss of vision. Over time, accumulation of toxic precursors may contribute to the death of retinal pigment epithelial cells and photoreceptor cell death by when the possibility to correct vision loss by voretigene neparvovec may be lost, with loss of its target cell population. Use of voretigene neparvovec in patients prior to loss of retinal pigment epithelial cells is intended to restore normal RPE65 protein function and so improve the patient's vision.

Pharmacology

Pharmacodynamics were investigated in main clinical studies by measurement of visual acuity, visual field depiction and by measurement of the sensitivity of the retinal to light. The results are described in the clinical efficacy section.

2.4.4. Discussion on clinical pharmacology

The investigation of clinical pharmacology was quite limited. However, this is acceptable in the context of a gene therapy for a rare disease that is administered directly to the sub-retinal space of each eye as a once-only surgical procedure.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology dossier submitted in support of Luxturna is acceptable.

The CHMP endorses the CAT assessment regarding the conclusions on the Clinical pharmacology as described above.

2.5. Clinical efficacy

2.5.1. Dose response study

Selection of the dose level employed (1.5E11 vg per eye) was based on a combination of non-clinical studies and the results of the Phase 1 studies (AAV2-hRPE65v2-101 and AAV2-hRPE65v2-102) which had indicated that a dose of 1.5E11 vg in a volume of 300 µl was safe and well tolerated in a similar patient population (the high dose was taken forward as all doses had similar safety profiles).

A dose-response effect could be neither established nor eliminated due to phenotypic variations of the subjects enrolled. In the absence of a dose response effect, the volume of 300 µl utilized for the Phase 1 high dose cohort targets a larger portion of the retina and thus provides a greater likelihood for direct benefit to the individual subjects.

Escalating beyond the dose of 1.5E11 vg per eye introduces greater potential for risk, including irreversible toxicity based on the nature of retinal cells, without clear evidence of greater potential for benefit. Delivery of volume larger than 300 µl, thereby reducing the concentration of the vector and

potentially facilitating further dose escalation, would complicate the surgical procedure, may increase the potential for prolonged retinal detachments, and would be more disruptive to the subjects in the days immediately following surgeries.

2.5.2. Main study

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

Study Participants

Inclusion criteria

- ≥ 3yrs old
- Visual acuity worse than 20/60 (both eyes) and/or visual field less than 20o in any meridian as measured by III4e isopter or equivalent (both eyes).
- Sufficient viable retinal cells as determined by non-invasive means such as OCT and / or ophthalmoscopy. Must have either:

1) an area of retina within the posterior pole of >100µm thickness shown on OCT

2) ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole

or

3) remaining visual field within 30o of fixation as measured by III4e isopter or equivalent

- Diagnosis of Leber's congenital amaurosis due to RPE65 mutations; confirmation of diagnosis of RPE65 mutations, by a CLIA-certified laboratory (homozygotes and compound heterozygotes were eligible)
- Subjects must be evaluable on mobility testing (the primary efficacy endpoint) to be eligible for the study.

Subjects who were able to pass the mobility course at Screening, in the time allotted, at the lowest illumination to be evaluated (1 lux) were to be considered too close to normal function with respect to ability to navigate in dim light conditions; these subjects were not eligible to enrol on the study.

Subjects who were unable to perform the mobility course at Screening with an accuracy score of ≤ 1 at the highest illumination to be evaluated (400 lux) were to be considered to have extensive disease progression such that they are less likely to achieve measurable, clinically meaningful benefit; these subjects were not eligible to enrol on the study.

Exclusion criteria

- 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

• Pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study

Treatments

Delivery of AAV2-hRPE65v2 used a standardised procedure optimised during the phase 1 dose-escalation and safety study. Vector administration was performed using a commercially available cannula designed for sub-retinal injection, the Bausch and Lomb Storz 39 gauge translocation cannula (Rancho Cucamonga, CA). Sub-retinal injection was performed after a standard 3-port pars plana vitrectomy.

The gene therapy material was administered in the ophthalmology surgical suite of each study site. Surgery was performed under general anaesthesia supplemented by retrobulbar anaesthetic to minimise intra-operative eye movement and postoperative discomfort. The site of the sub-retinal injection was in the post-equatorial retina within the posterior pole. An area approximately one third to one fourth of the total retinal area was targeted. This site was selected to maximise the potential that viable retinal cells were exposed to the vector.

Provided that the condition of viable retinal cells was met, the extent of the injection included a portion of the macular area, as this is the region that normally provides the highest degree of visual function and sensitivity and thus successful treatment of this area was predicted to result in the greatest therapeutic effect.

Objectives

The primary objective was to determine whether non-simultaneous, bilateral sub-retinal administration of AAV2-hRPE65v2 improved the ability to navigate (as measured by mobility testing) in adults and children, three years of age or older, with RPE65 mutations.

The secondary objective of this study was to continue to assess the safety and tolerability of AAV2-hRPE65v2 administrations.

Outcomes/endpoints

The primary efficacy endpoint was the subject's bilateral performance (no eye patching) on the mobility test, as measured by a change score, one year following vector administration as compared to a subject's Baseline bilateral mobility test performance.

Secondary efficacy outcomes were:

- Full-field sensitivity threshold testing: Average light sensitivity (averaged over both eyes) for white light at Year 1B/C as compared to Baseline light sensitivity testing
- Monocular mobility testing change score: Change from Baseline to Year 1B/C in the score of the mobility testing for the first eye
- Visual acuity: Average change in visual acuity (averaged over both eyes) at Year 1B/C as compared to Baseline

For FST, a subject's response is light sensitivity as measured in decibels (dB) which was converted to the logarithm of candela second per square meter (log10[cd.s/m2]) to accommodate different dB conversion rates.

Visual acuity was converted to the logarithm of the minimum angle of resolution (LogMAR).

Analyses of FST and VA were based on longitudinal models that provided estimates of the difference between Baseline and Year 1B/C. For the monocular mobility testing, analyses used models analogous to the model described for the primary outcome.

Sample size

At least twenty-seven subjects, three years of age or older, were to be recruited at either The Children's Hospital of Philadelphia (Site 001) or University of Iowa (Site 005).

Randomisation

Study 301 subjects were randomized in a 2:1 ratio to the Intervention or the Control group, stratified by Screening age (≥ 10 years or < 10 years) and mobility testing category (passing at ≥ 125 lux or passing at < 125 lux).

Stratification was considered important due to the variability of the patient population (e.g., age, disease-causing mutation, sequence variants in other retina-specific genes, extent of retinal degeneration, clinical history, and clinical presentation [range of functioning or vision loss]) and small sample size of the study.

In an effort to balance the Intervention and Control groups, the age and mobility testing performance cut-offs were chosen based on expected age of study participants given the study site lists of interested patients and based on experience with mobility testing of participants in the Phase 1 studies for AAV2-hRPE65v2, as well as the initial observations from the MTVS study.

Blinding (masking)

The Phase 3 study was open-label, rather than a double-masked placebo-controlled trial, as the use of a sham-sub-retinal surgery group as the concurrent control arm was rejected for ethical reasons, particularly given the inclusion of paediatric participants.

One of the main risks of the study was general anaesthesia required for surgical intervention. Additionally, though vitrectomy is a routine procedure for surgeons with vitreo-retinal surgical training, surgical complications (including infection) are known to occur. Given the risks associated with sham-sub-retinal surgery, and the lack of a prospect of direct benefit for subjects randomized to such a control group, the Applicant determined a delayed-intervention control group was more ethically appropriate than a masked, sham-subretinal surgery group. Thus, masking procedures were considered important to support the validity of the study results.

To mitigate the potential for bias and to support the validity of the study results, groups independent from both the applicant and the clinical study teams scored and analysed the primary efficacy endpoint (mobility testing).

Graders of the mobility testing were independent from the study team and had received training. These individuals received coded mobility testing videos on a weekly basis and received no information about the subjects, visit schedule, treatment group, results of any other retinal/visual function testing, or even the identity of the clinical study (as the applicant utilizes this Video Reading Center for more than one study).

An independent data management group assigned the video's code and the masked sequence in which videos were presented so that graders did not know whether the video they were evaluating was a Baseline evaluation or a follow-up evaluation for any given subject.

Statistical methods

The primary efficacy analysis was to use a non-parametric permutation test based on a Wilcoxon rank-sum as the observed test statistic and an exact method for the corresponding p-value. The planned approach was to randomize the allocation of treatment label to subject and, for a large number of replications, to calculate the test statistic from the Wilcoxon rank-sum test. The p-value from the permutation test was to be the proportion of p-values that were smaller than the value observed in the actual dataset. The Wilcoxon rank-sum test statistic was to use the average rank when observations had the same value (i.e., were tied).

The permutation test was to sample 10,000 times from the distribution of possibilities. However, when following the actual blocked randomization to determine this distribution, the total number of permutations was less than 10,000 for both the ITT and mITT analysis populations. Therefore, the randomization test used the set of all possible permutations.

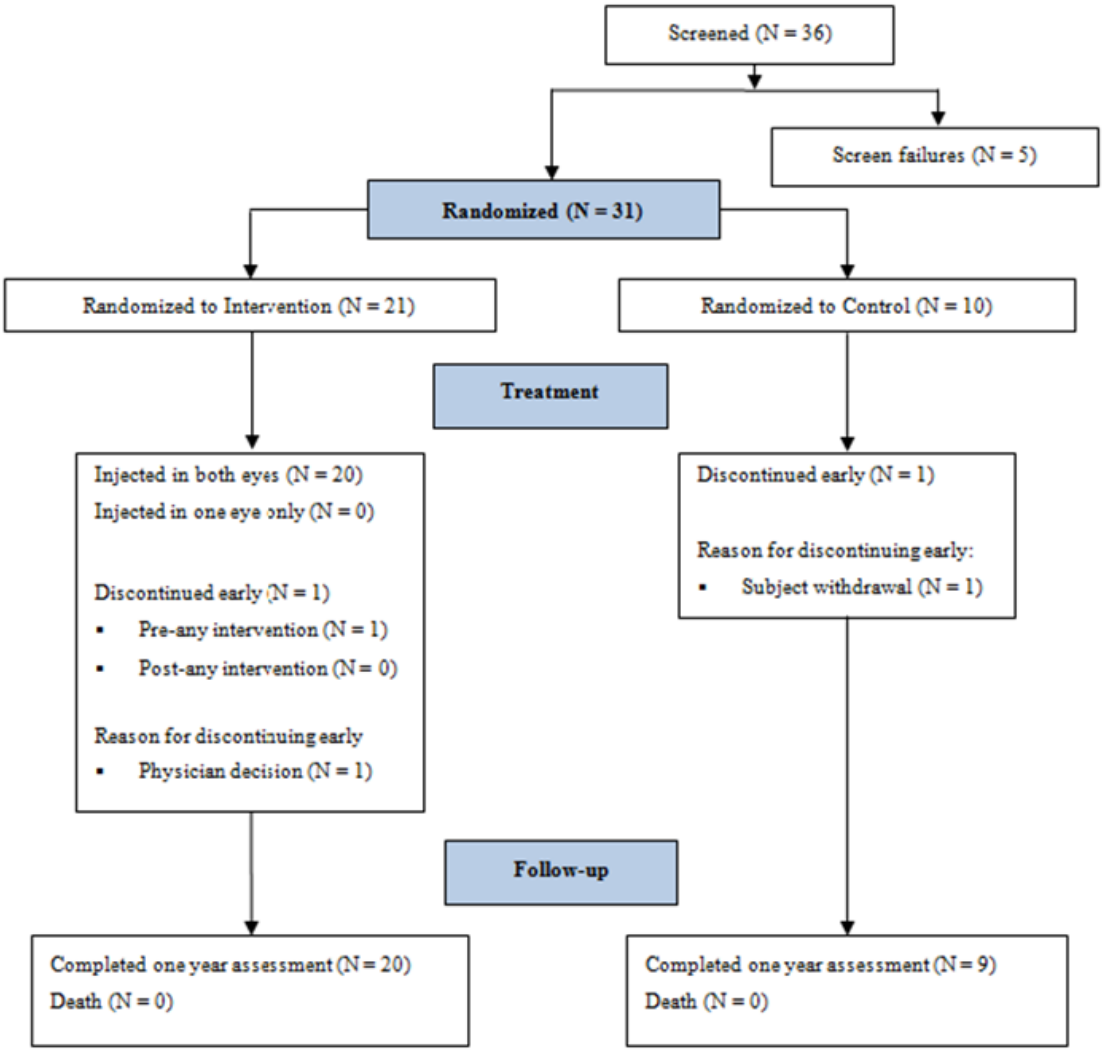
The primary efficacy outcome was to be tested at a two-sided Type I error rate of 0.05. Unless mentioned otherwise, all other statistical tests were to use two-sided significance criteria of $\alpha = 0.05$. Confidence intervals were to be two-sided.

While the primary interest of this study was the performance of the subjects at Year 1B (Intervention) and Year 1C (Control), the pattern of response over time was also considered to be relevant to understanding the effects of the therapy, as well as the effects of non-intervention (natural history). Exploratory analyses were to examine change over time.

Results

Participant flow

Figure 2 Subject Disposition



Recruitment

Study Initiation Date: 15-Nov-2012

Study Completion Date: 06-Apr-2015 (last subject, last visit)

31 subjects were recruited at 2 hospital sites in the USA; 29 subjects were exposed to study drug.

Conduct of the study

Protocol deviations were recorded in 22 (71%) subjects, including 17 (81%) subjects in the Intervention group and five (50%) subjects in the Control group. They are not considered likely to affect overall conclusions of the study.

Baseline data

Population

Overall, 31 subjects were randomized into the study AAV2-hRPE65v2-301, including 21 Original Intervention subjects and 10 Original Control subjects. A summary of subjects by study site is shown in the following table:

Table 1 Enrolment by Study Site and Strata (ITT)

Parameter, n (%)	Intervention (N = 21)	Control (N = 10)	Total (N = 31)
Site			
Children's Hospital of Philadelphia, United States	11 (52%)	8 (80%)	19 (61%)
University of Iowa, United States	10 (48%)	2 (20%)	12 (39%)
Strata: Age (at Screening)			
Age < 10 years	9 (43%)	4 (40%)	13 (42%)
Age ≥ 10 years	12 (57%)	6 (60%)	18 (58%)
Strata: Mobility testing level (at Screening) [a]			
Pass at < 125 lux	12 (57%)	4 (40%)	16 (52%)
Pass at ≥ 125 lux	9 (43%)	6 (60%)	15 (48%)

Column header counts and denominators are subjects in the ITT population.
[a] As determined by the eye with the worst passing result
Data Source: Table 14.1.1.1, Listing 16.2.4.1 and Listing 16.2.6.1.3.

Enrolment into the Intervention group was evenly divided across the CHOP and Iowa sites (52% and 48%, respectively). For the Control group, more subjects were enrolled by CHOP as compared to Iowa (80% and 20%, respectively).

Study enrolment was stratified by subject age (< 10 years and ≥ 10 years) and Screening mobility testing level (pass at < 125 lux and pass at ≥ 125 lux). In cases where unilateral differences in the mobility testing results at Screening were observed, the worse eye was used for stratification.

For the Intervention group, subjects were relatively evenly divided across age strata (43% < 10 years of age; 57% ≥ 10 years of age) and Screening mobility (57% pass at < 125 lux; 43% pass at ≥ 125 lux. Similar strata characteristics were seen in the Control group, with 40% of subjects < 10 years of age and 40% of subjects passing the Screening mobility testing procedures at < 125 lux.

Numbers analysed

Data sets

A summary of the study analysis populations is presented in the following table:

Table 2 Analysis Populations (All Randomized Subjects)

Analysis Sets	Intervention (N = 21)	Control (N = 10)	Overall (N = 31)
Randomized, n (%)	21 (100%)	10 (100%)	31 (100%)
Intent-to-Treat (ITT) Population [a]	21 (100%)	10 (100%)	31 (100%)
Modified Intent-to-Treat (mITT) Population [b]	20 (95%)	9 (90%)	29 (94%)
Safety Population [c]	20 (95%)	9 (90%)	29 (94%)
Per-Protocol (PP) Population [d]	19 (90%)	9 (90%)	28 (90%)

[a] Includes all randomized subjects.

[b] Includes all randomized subjects who did not withdraw, or were not withdrawn, prior to any of the following people knowing the treatment assignment: the subject, parent, Principal Investigator, or Medical Monitor. Subjects in the mITT population were categorized by their randomized treatment assignment.

[c] Includes all randomized subjects who received injection in either eye for the Intervention group and all Control group subjects who did not withdraw, or were not withdrawn, prior to any of the following people knowing the treatment assignment: the subject, parent, Principal Investigator, or Medical Monitor.

[d] Includes all ITT population subjects who 1) met all inclusion and exclusion criteria and 2) did not withdraw, or were not withdrawn prior to the subject, parent, Principal Investigator, or Medical Monitor knowing the treatment assignment. For the Intervention group, the PP population excluded subjects who did not receive both injections.

Source data: Table 14.1.1.5 and Listing 16.2.3.

Outcomes and estimation

The primary efficacy outcome was the performance on the Mobility Test as measured by a change score one year following vector administration (Intervention subjects), or one year following Baseline (Control subjects), as compared to a subject's Baseline mobility test performance, under the bilateral eye-patching testing scenario.

In general, a subject may be classified as having improved, stable, or worsened ability to navigate under low light conditions. The mobility testing protocol used in Phase 1 studies of AAV2-hRPE65v2 was expanded to include testing under mesopic (lower light) conditions, the conditions that elicit responses from both rod and cone photoreceptors. The test design was also refined such that courses were standardized to contain a specified number of turns and numbers of specific types of obstacles, as was the videotaping protocol thereby enabling more accurate scoring of the tests by trained, independent graders.

To optimize and ensure greatest consistency of mobility testing procedures, the following changes were implemented during the standardization process:

1. Testing was to be carried out at Baseline to determine the estimated lower light level (for each eye) at which a subject could carry out mobility testing;
2. Light levels were standardized to a pre-determined series of specified light levels;
3. The course was standardized so that both intra-subject and inter-subject test results could be compared more accurately;
4. Twelve different test configurations with comparable difficulty in terms of distance, number of turns, and number of obstacles were developed and these are selected randomly for each test in order to minimize any learning effect;
5. Procedures with which to document (videotape) the test performance were optimized;
6. Detailed instructions as to how to carry out Baseline and post-injection mobility testing, and on how to score the tests, were assembled into a standard operating procedure;
7. The scoring paradigm to be used, namely weighting the accuracy and speed for each test according to a defined algorithm that places greater emphasis on accuracy than speed, included accuracy and time penalties, but removed identification of landmarks (essentially required for the timely and accurate completion of the course); and
8. Independent masked readers scored all video recordings.

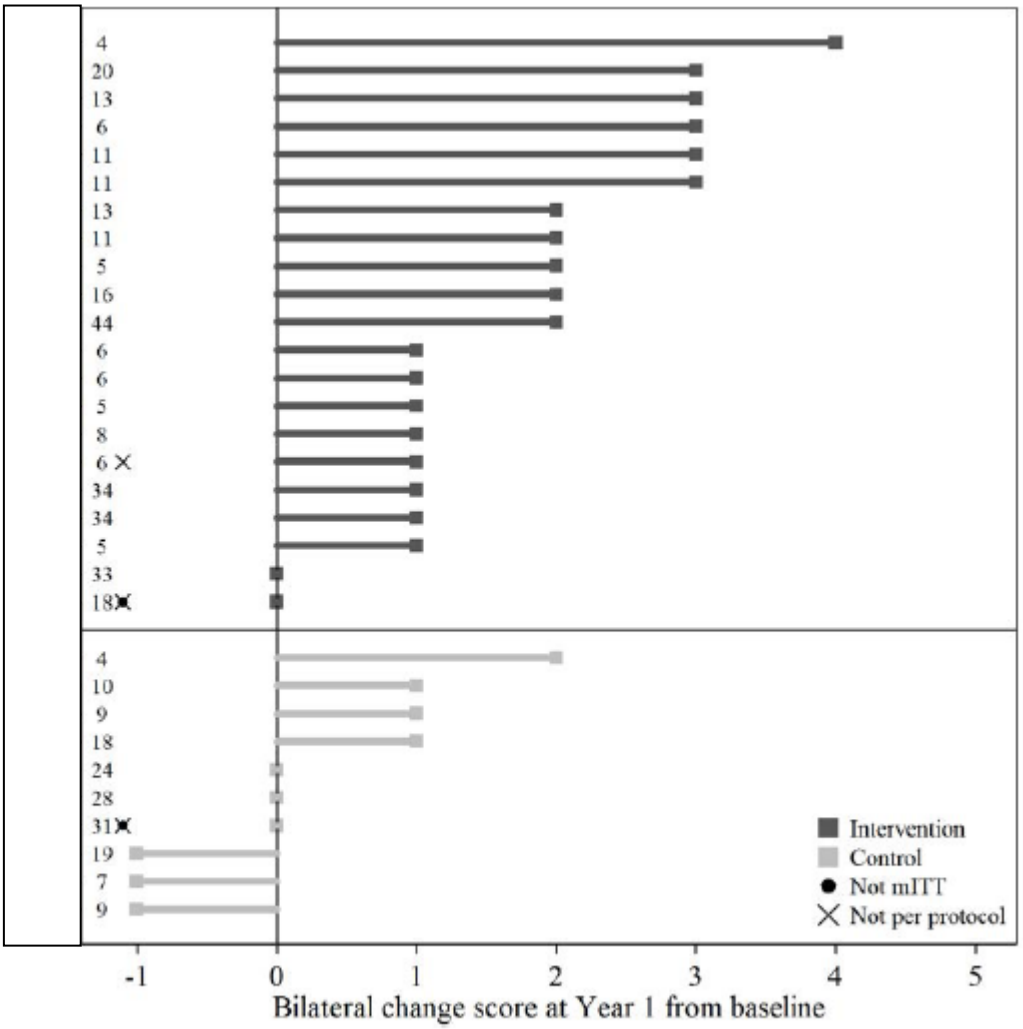
The testing rooms at the two study sites were established in parallel, using the same configuration of LED and incandescent lighting panels to achieve pre-set (programmed) luminances; the precise panel settings used for the pre-set luminances accommodated differences in room height between the sites. Each room was evaluated, using multiple calibrated light meters as well as specialized photometer/radiometer equipment, prior to study start and determined to be remarkably similar with respect to the seven specified light levels. Throughout the study, the pre-set luminances were continually evaluated by the placement of calibrated light meters at five places on the course (center and four corners).

Following a 40-minute dark adaption, each subject was to be tested under at least two and sometimes three or more different (specified) lighting conditions for each eye and then with both eyes open (at least six test runs). The levels of light, selected to span lighting conditions that individuals encounter in daily life, were to range from a studio with floodlights (400 lux) or a brightly lit office (250 lux) down to a poorly lit sidewalk at night (1 lux). The estimated light sensitivity cut-off was to be determined for each subject for each eye following testing at levels including 1, 4, 10, 50, 125, 250, or 400 lux (going from dimmest to brightest). More than six tests per subject, per visit were to be performed if the subject's estimated light sensitivity cut-off at Baseline differed from one eye to the other. The course was to be reconfigured between each attempt, using twelve standardized templates, to reduce the impact of a potential learning effect.

At the first follow-up visit after Baseline, mobility testing was to be carried out using the light sensitivity cut-off identified at Baseline and at lighting conditions just below this cut-off (sub-sensitivity cut-off light level). For example, if the light sensitivity cut-off at Baseline was 125 lux, follow-up testing was to be carried out at 125 lux and 50 lux.

Results are summarised in the following figure:

Figure 3 Bilateral MT Change Scores at Year 1 from Baseline, by Individual (ITT)



Age at Randomization displayed next to the Subject ID.
Data Source: Figure 14.2.1.1, Listing 16.2.6.1.1 through Listing 16.2.6.1.4.

Two subjects had missing data affecting the primary outcome (only Baseline data was available since they were removed from the study on the day of randomization and prior to any intervention). As specified in the SAP, these subjects were assigned a change score of 0 at Year 1 for both bilateral and unilateral tests.

Statistical analysis is presented in the following table:

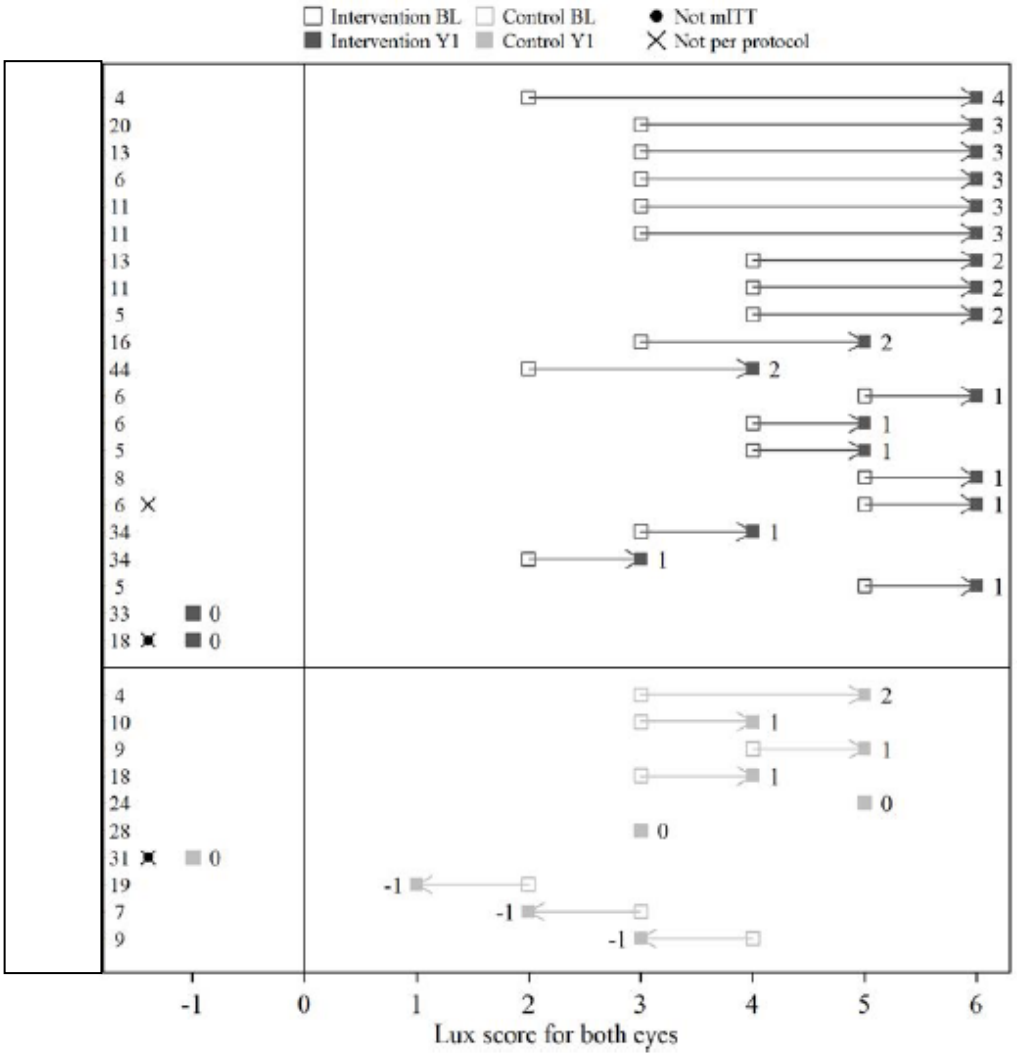
Table 3 Bilateral MT Change Score, Year 1 Compared to Baseline (ITT)

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

Column header counts are subjects in the ITT population. The observed two-sided *p*-value is from a Wilcoxon rank-sum test using an exact method. The permutation test *p*-value was computed from all possible permutations.
Data Source: Table 14.2.2.1, Listing 16.2.6.1.1 through Listing 16.2.6.1.4.

Figure 4 presents the Baseline and Year 1 bilateral lux score for each subject:

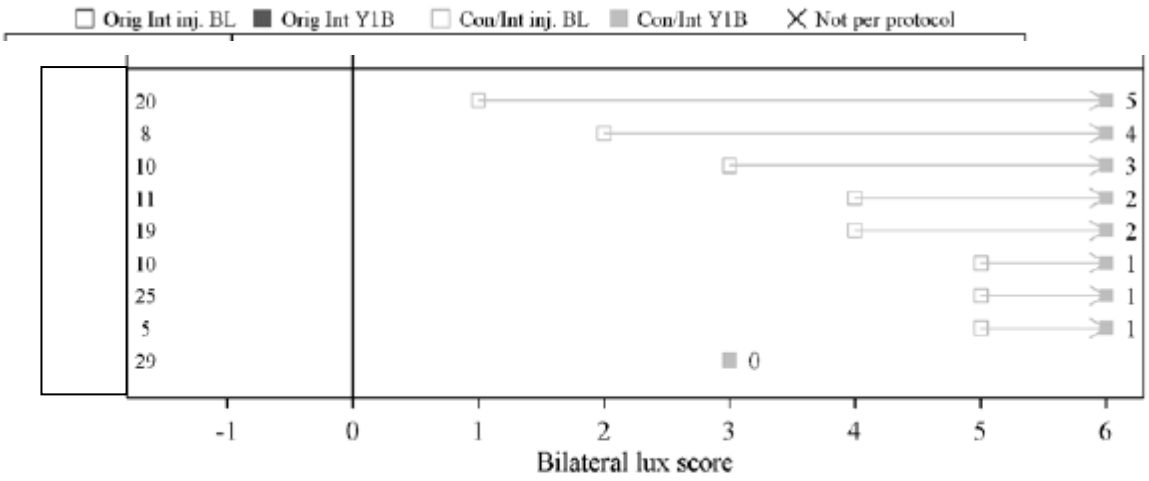
Figure 4 Bilateral MT Scores at Baseline and Year 1, by Individual (ITT)



BL, Baseline. Age at Randomization displayed next to the Subject ID; change score displayed next to the Year 1 lux score.
Data Source: Figure 14.2.1.2, Listing 16.2.6.1.1 through Listing 16.2.6.1.4.

Arrows show the direction of either improvement or decline, as seen in three Control subjects. In this figure, the age at randomization is displayed next to the Subject ID and the change score is displayed next to the Year 1 lux score [the highest score possible is '6'].

Figure 5 Bilateral MT Scores at Injection Baseline and Year 1B, by Individual (mITT)



Con/Int, Control / Intervention; Orig Int, Original Intervention. Age at first injection is displayed next to the Subject ID; change score is displayed next to the Year 1B lux score.

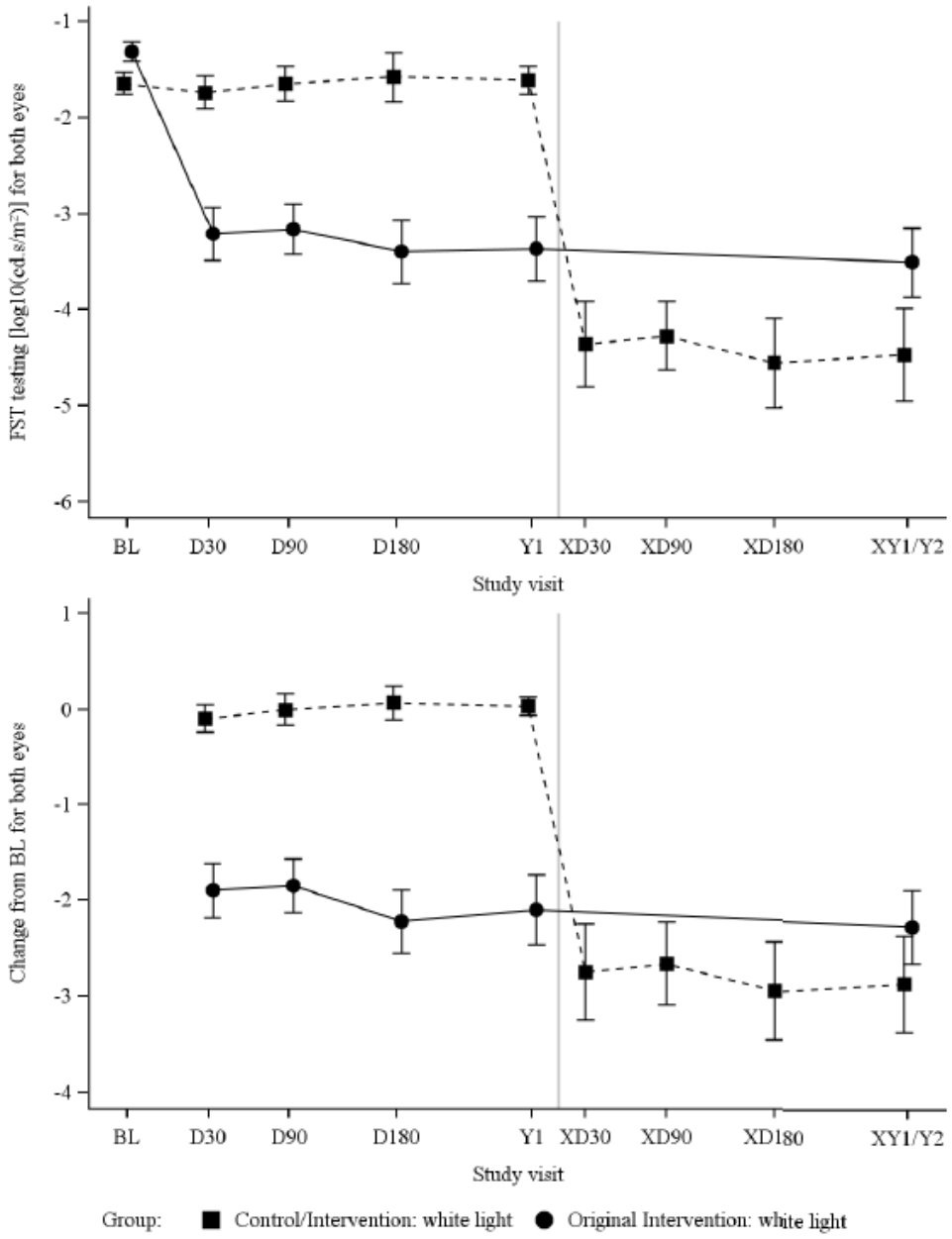
Data Source: Figure 14.2.1.2, Listing 16.2.6.1.1 through Listing 16.2.6.1.7.

Secondary endpoints

Full-field light sensitivity

Full-field light sensitivity testing measures the light sensitivity of the entire visual field by recording the luminance at which a subject reports seeing the dimmest flash and can be carried out in subjects with poor visual acuity, small visual fields, and nystagmus.

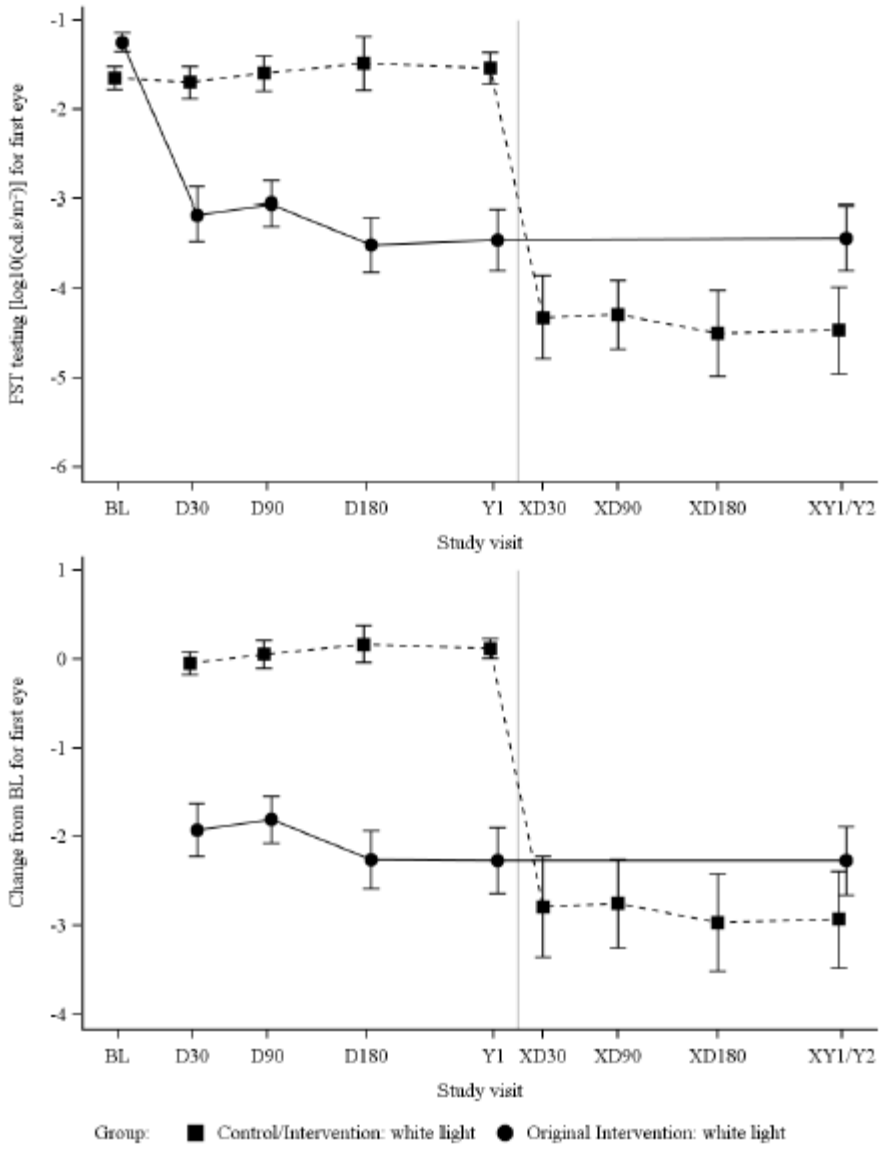
Figure 6 FST White Light, Observed Means over Time, Both Eyes (mITT)



BL, baseline; cd.s/m^2, candela second per meter squared; FST, full-field sensitivity testing (white light); X, cross over. Data presented as mean ± SE. For Control / Intervention, change is relative to injection baseline after Year 1.
Data Source: Figure 14.2.2.1 and Listing 16.2.6.2.1 through Listing 16.2.6.2.5.

Results are also shown separately for 1st and 2nd eyes exposed:

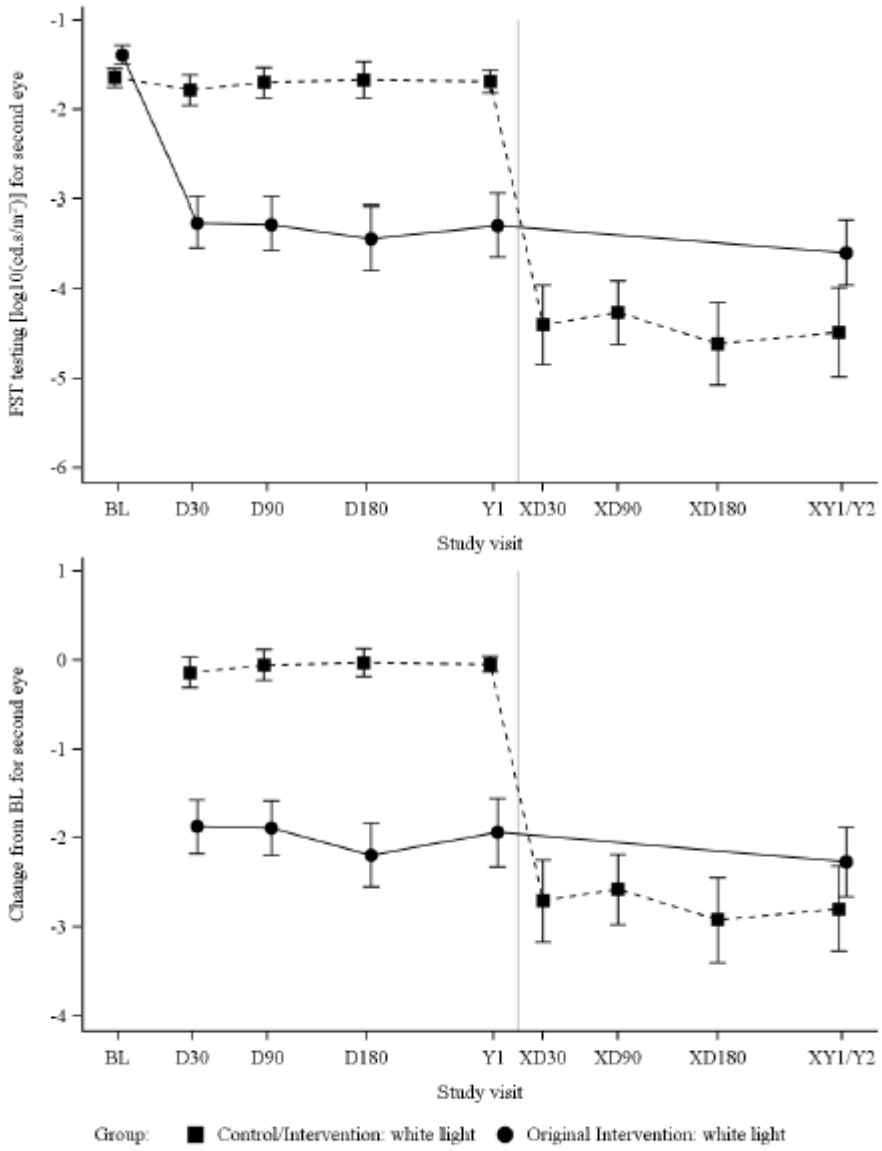
Figure 7 FST White Light, Observed Means Over Time, First Eye mITT/Safety Population (N-29)



Abbreviations: BL=baseline; cd.s/m²=candela second per meter squared; FST=full-field light sensitivity threshold; X=crossover. Intervals are +/- 1 standard error. For Control/Interventions, change is relative to injection baseline after Year 1.

Database lock: 2016-06-23
E:\proj\Spark 301-302\programs\f_ff.sas v.002 (last run: 09/07/2016, 17:14) f_ffwMITT1st.rtf

Figure 8 FST White Light, Observed Means Over Time, Second Eye mITT/Safety Population (N=29)



Abbreviations: BL=baseline; cd.s/m²=candela second per meter squared; FST=full-field light sensitivity threshold; X=crossover. Intervals are +/- 1 standard error. For Control/Interventions, change is relative to injection baseline after Year 1.

Database lock: 2016-06-23
E:\proj\Spark 301-302\programs\f_ff.sas v.002 (last run: 09/07/2016, 17:14) f_ffwMITT2nd.rtf

Visual acuity

Visual acuity, or best-corrected visual acuity, measures were to document any change in central vision, the ability to resolve standard optotype images presented as optotypes/letters corresponding to different visual angles i.e. image size.

At one year after exposure to voretigene neparvovec, improvement in visual acuity of at least 0.3 LogMAR occurred in 11 (55%) of the first-treated eyes and 4 (20%) of the second-treated eyes; no one in the control group displayed such an improvement of visual acuity in either the first or second eye.

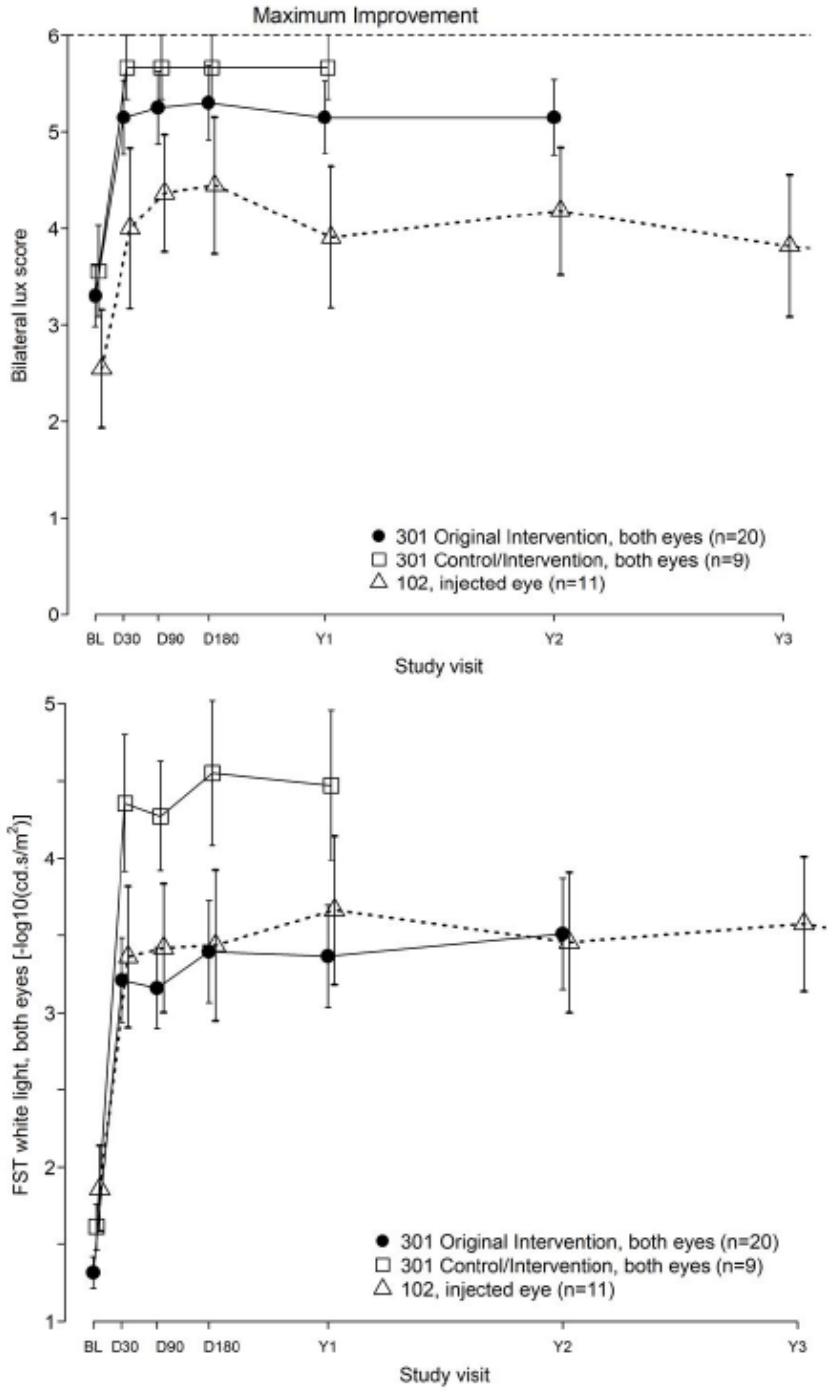
Ancillary analyses

Durability of the Treatment Effect

Overall, the available clinical efficacy data to date support an onset of AAV2-hRPE65v2 treatment effect by approximately 30 days post-administration with durable improvements in visual function that are maintained for at least one year. For Study 301 / 302, subjects in the Original Intervention group have demonstrated durable improvements in visual performance across multiple endpoints for at least two years following AAV2-hRPE65v2 administration. Similarly, subjects in the Control / Intervention group, once injected with AAV2-hRPE65v2, have demonstrated a comparable onset and durability in visual performance improvements to those observed in the Original Intervention group, through at least one year following bilateral AAV2-hRPE65v2 administration.

As a supportive analysis, combined presentations of the bilateral MLMT and FST scores, means over time, for Study 301 / 302 and Study 102 are provided in the following figure:

Figure 9 Bilateral MLMT and FST Results Across Studies



BL = injection baseline; D = Day; Y = Year; FST = full-field light sensitivity threshold; MLMT = multi-luminance mobility test. Intervals are ± SE. mITT population for Study 301 (Original Intervention, n = 20; Control / Intervention, n = 9); Study 102, n = 11.

Data Source: Study 301 CSR Addendum 2016, Listing 16.2.6.1.6 and Listing 16.2.6.2.5; Module 5.3.5.3, Study 102, Listing 16.2.6.3.1.

As seen in Figure 9, for both MLMT (upper panel) and FST (lower panel), the onset and durability of the treatment responses across Study 301 / 302 and Study 102 were similar. More specifically, for both endpoints, marked improvements were observed by approximately 30 days post-administration for each study and the respective treatment effects were maintained across the evaluated time periods, with a durable mean change from injection baseline seen from one to three years post-vector administration.

Overall, for both Phase 3 and Phase 1, the observed mean improvements in functional vision, light sensitivity, and visual function suggest consistent, durable treatment of vision loss following AAV2-hRPE65v2 administration, through at least three years for Phase 1 subjects and for up to two years in Phase 3 subjects, with observation ongoing.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 4 Summary of Efficacy for trial 301 / 302

Title: A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE)		
Study identifier	AAV2-hRPE65v2-301 / 302	
Design	Open-label, randomized Delayed entry design for subjects assigned first to control group	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	1 year Subjects in the control group were followed for 1 year before exposure to study drug Subjects will be followed for 15yrs
Hypothesis	Not stated	

Treatments groups	Intervention group	21 subjects Single sub-retinal administration of 1.5E11 vg AAV2-hRPE65v2 to each eye. [1 subject in the intervention group did not receive study drug]
	Control group	10 subjects Followed up for 1 year before exposure to study drug / efficacy endpoints measured in this control time [1 subject in the control group did not receive study drug]
		Study drug administered after 1 year observation

Endpoints and definitions	Primary endpoint	MLMT	**Multi-luminance mobility test (MLMT)**: subject's performance (no eye patching) on the mobility test using binocular vision, as measured by a change score, one year following vector administration as compared to a subject's Baseline performance. The mobility test tool is a clinic-based clinician-reported outcome assessment tool. Subjects are asked to navigate between start and finish in a stylised obstacle course at ambient light set at one level between 400 lux and 1 lux during each attempt. The main analysis was of binocular navigation of the test layout. Subjects are marked as either 'pass' or 'fail'; a 'pass' mark requires the subject to complete the task within 180 secs and to 'fail to navigate' 3 or less obstacles. A 'pass' mark at 1 lux is the highest possible score. The tool returns ordinal scores of between -1 and +6 (pass at 1 lux).
	Secondary endpoints	FST	**Full-field sensitivity threshold** testing: Average light sensitivity of the entire visual field for white light at Year 1 after exposure as compared to Baseline light sensitivity testing. Testing was done with the Diagnosys / Espion system on subjects with dilated eyes in a dark-adapted state and seated in front of a Ganzfeld dome in which light flashes are generated.

		Monocular MLMT	**Monocular mobility testing** change **score**: Change from Baseline to Year 1 in the score of the mobility testing for the first eye
		VA	Average change in **visual acuity** (averaged over both eyes) at Year 1 as compared to Baseline.
Database lock	16 July 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The main population for efficacy was the intent to treat population 1 year after exposure		
Descriptions of outcomes	**Change in MLMT score** 1 year after exposure and using **binocular vision**	Difference (95% CI) Intervention-Control	p-value
		1.6 (0.72, 2.41)	0.001
Analysis description	**Secondary analyses**		

Descriptions of outcomes	**Full-field light sensitivity test** results using white light [Log10(cd.s/m2)]: First assigned eye (ITT) Intervention, N = 21 Baseline / Year 1 / Change N: 20 / 20 / 19 Mean (SE): -1.23 (0.10) / -3.44 (0.30) / -2.21 (0.30) Control, N = 10 N: 10 / 9 / 9 Mean (SE): -1.65 (0.14) / -1.54 (0.44) / 0.12 (0.45) Difference (95% CI) (Intervention-Control) -2.33 (-3.44, -1.22), p<0.001 Second assigned eye (ITT) Intervention, N = 21 Baseline / Year 1 / Change N: 20 / 20 / 19 Mean (SE): -1.35 (0.09) / -3.28 (0.29) / -1.93 (0.31) Control, N = 10 N: 10 / 9 / 9 Mean (SE): -1.64 (0.14) / -1.69 (0.44) / 0.04 (0.46) Difference (95% CI) (Intervention-Control) -1.89 (-3.03, -0.75), p<0.002

	Change in MLMT score 1 year after exposure and using **monocular vision**	Difference (95% CI) Intervention-Control	p-value
	using assigned first eye only	1.7 (0.89, 2.52)	0.001
	using assigned second eye only	** company requested to submit data	** company requested to submit data
	Visual acuity: at one year after exposure to voretigene neparvovec, improvement in visual acuity of at least 0.3 LogMAR occurred in 11 (55%) of the first-treated eyes and 4 (20%) of the second-treated eyes; no one in the control group displayed such an improvement of visual acuity in either the first or second eye.		

Supportive studies

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

Study Number: AAV2-hRPE65v2-101

A phase I study

Study Design: Open-label dose-escalation safety study

Study Initiation Date: 25 September 2007
Study Completion Date: 14 October 2014 (data cut-off date)
Report Date: 23 October 2015
Amendment dates: Amendment 001, 19 October 2016; Amendment 002, EU, 08 June 2017
Population: 12 subjects (7 male, 5 female) ages 8 to 44yrs with Leber's congenital amaurosis and visual acuity ≤20/160 or visual field less than 20° in the eye to be injected

Intervention: AAV2-hRPE65v2 by direct injection to the sub-retinal space. 3 doses were chosen: the low (1.5E10 vg) and middle (4.8E10 vg) dose cohorts were administered in a volume of 150 µL and the high dose (1.5E11 vg) was administered in a volume of 300 µL.
Each subject received a one-time sub-retinal injection of AAV2-hRPE65v2 into a single eye (eye with worse function).

Comparator: none

Outcomes: Subjects have been followed up for 8 years.
10 (83%) subjects experienced TEAEs considered related to the study drug administration e.g. eye irritation and hyperaemia, one instance of macular hole.
Efficacy endpoints included assessments of visual acuity, full field light sensitivity, pupillometry and mobility testing (a version of the test that accompanied study 301/2)

Mobility testing was designed to approximate real life orientation and mobility in a clinical setting.
The mobility testing protocol was refined over the course of the study, as reflected in the pre- and post-standardization listings, and this affects both the interpretation of the results and the number of subjects considered evaluable.
The first four subjects (NP-01, NP-02, NP-03, and NP-04) were considered non-evaluable given the inconsistent use of patching, as well as the variability of lighting conditions and test course difficulty.
Differences between the injected and un-injected eyes, or between Baseline and follow-up testing with the injected eye, were not readily observed for CH-06, CH-11, CH-12 or CH-13.
Both CH-12 and CH-13, the oldest individuals in the study and the most advanced in terms of disease progression, did not pass any mobility testing runs over the course of the study.

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

Study Number: AAV2-hRPE65v2-102
A phase I study

Study Design: Open-label safety study
Study Initiation Date: 15 Nov 2010
Study Completion Date: 14 October 2014 (data cut-off date)
Report Date: 23 October 2015
Amendment 001 Date: 09 June 2017
Population: subjects who had taken part in initial Phase 1 study (101) with unilateral, sub-retinal administration of AAV2-hRPE65v2. One subject was not eligible for Study 102 study owing to glaucoma in the un-injected eye.

Intervention: All subjects received 1.5E11 vector genomes (vg) of AAV2- hRPE65v2 delivered to the sub-retinal space of the previously un-injected, contralateral eye. This was the 'high dose' of study 101.

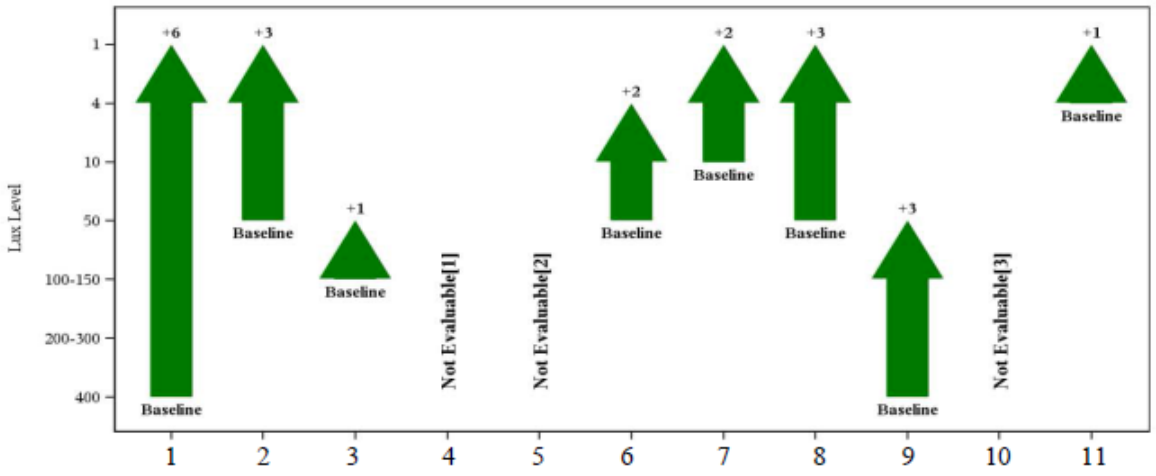
Comparator: none / comparison was made to previously injected eye

Outcomes: The cumulative subject follow-up after AAV2-hRPE65v2 administration for the Phase 1 studies ranges from five to seven years for efficacy endpoints and from six to eight years for safety endpoints.

One serious adverse event of poorly controlled raised intraocular pressure leading to atrophy of the optic nerve. 8/11 subjects showed improvements in full field sensitivity thresholds and mobility in low ambient light.

One subject was not evaluable on mobility testing (did not have a pass or an accuracy score of <1 at the highest light levels evaluated at 102 baseline) and would not have been eligible for the Phase 3 study prior to the participation in the Phase 1 studies.

Figure 10 Results of Mobility Testing – Change from Baseline to Year 1 (Efficacy Population)



[1] Participant 4 could pass the mobility test at 1 Lux at 102 Baseline and would not qualify for inclusion in Phase 3.

[2] Participant 5 performance was atypical, likely due to known sequence variant in the retina-specific *RDH-12* gene and / or optic nerve head drusen present at 101 Baseline.

[3] Participant 10 failed mobility testing at the highest light level tested at 102 Baseline. Though not tested at 400 lux, as it was pre-Oct-2011, it is believed that Participant 10 would not qualify for inclusion in Phase 3. Source data: Graph 14.2.12.

Light sensitivity remained essentially stable in three subjects.

Pupillary light reflex: at Year 2, apparent improvement could not be observed in one subject.

Study title: Natural History of Individuals with Retinal Degeneration Due to Autosomal Recessive Mutations in the RPE65 Gene
Study code: RPE65 NHx (amendment 001, EU)

Study Design: Retrospective medical chart review

Study Initiation Date: 28 July 2014

Study Completion Date: 05 Feb 2016

Report Date: 12 June 2017

Rationale for study

Mutations in the human retinal pigment epithelium 65 gene (RPE65) result in progressive visual deterioration, leading inexorably to blindness, with the onset of symptoms typically occurring early in life.

Leber congenital amaurosis is a clinical diagnosis commonly associated with mutations in the RPE65 gene, but other similar clinical diagnoses, such as Retinitis Pigmentosa and various iterations of Early Onset Retinal Dystrophy have also been attributed to mutations in this gene.

Since retinal disease caused by mutations in the RPE65 gene is relatively uncommon, the existing body of information describing the natural history and disease course is somewhat limited. This retrospective descriptive study was designed to ascertain the natural history of the disease and clinical course in individuals with retinal degenerative disease caused by mutations in RPE65.

This study collected clinical data from seven tertiary referral centres for retinal degenerative diseases worldwide, with the objective of determining the degree and rate of disease progression over time by evaluating various clinical data points, including VA testing, VF testing, optical coherence tomography and other visual function parameters from a large cohort of subjects.

Study objectives

To describe the natural history of retinal degenerative disease in subjects with mutations in the RPE65 gene utilizing longitudinal ocular history review and clinical testing, including assessments of visual acuity, visual fields, colour vision and light sensitivity, when available. In addition, optical coherence tomography (OCT), electroretinograms (ERG), and dilated fundus examinations with retinal imaging and comprehensive ophthalmic exam data were also collected.

The main objectives were to obtain data on visual acuity, Goldmann kinetic visual fields and optical coherence tomography.

Population

Inclusion criteria

Subjects (medical records) had to meet the following inclusion criteria to be eligible for participation in the study:

- Males or females born between January 1, 1963 and December 31, 2010 (inclusive)
- Genetic diagnosis consistent with autosomal recessive mutation(s) in the RPE65 gene
- Minimum of two office visits/clinic encounters occurring prior to the following:
  a) Retinal surgery or surgery that penetrated the posterior chamber (e.g., vitrectomy, trabeculectomy, glaucoma filtering surgery, and retinal device implantation)
  b) Enrolment in an interventional study for inherited retinal degenerations (i.e., surgical, device, and/or study drug interventional studies).

Exclusion criteria

- Other retinal disease or diseases that affect retinal function
- Systemic diseases associated with mutations in retinal genes

Disposition of subjects is summarised in the following table:

Table 5 Disposition of Subjects (All Subject Charts)

Category, n (%)	Eligible (N=70)	Ineligible (N = 32)	Total (N = 102)
Eligible	70 (100.0)	0	70 (68.6)
Completed Study[a]	70 (100.0)	0	70 (68.6)
Reasons for Screen Failure			
Born outside of date range	0	17 (53.1)	17 (16.7)
No diagnosis of *RPE65* mutation	0	1 (3.1)	1 (1.0)
Did not meet minimum visit number[b]	0	22 (68.8)	22 (21.6)
Other retinal disorders or mutations	0	1 (3.1)	1 (1.0)
Other eye disorders impacting retina	0	1 (3.1)	1 (1.0)
Systemic diseases associated with mutations in other genes	0	0	0
Only one office visit/encounter	0	23 (71.9)	23 (22.5)

[a] Completed study denotes that data were abstracted from the individual subject chart. All charts that were "eligible" had data extracted.

[b] Needed a minimum of two visits *prior to* 1) retinal or posterior chamber surgery or 2) participation in an interventional clinical trial for IRD.

Source data: Table 14.1.1; Listing 16.2.1; Listing 16.2.2

Enrolment by site is shown in the following table:

Table 6 Enrolment by Site

Site, n (%)	Eligible (N=70)	Ineligible (N = 32)	Total (N = 102)
01 Belgium (Ghent)	13 (18.6)	4 (12.5)	17 (16.7)
02 Germany (Giessen)	13 (18.6)	5 (15.6)	18 (17.6)
03 Massachusetts, USA (Boston)	3 (4.3)	7 (21.9)	10 (9.8)
05 Denmark (Copenhagen)	18 (25.7)	4 (12.5)	22 (21.6)
06 Oregon, USA (Portland)	14 (20.0)	3 (9.4)	17 (16.7)
07 Brazil (Sao Paulo)	3 (4.3)	5 (15.6)	8 (7.8)
08 France (Montpellier)	6 (8.6)	4 (12.5)	10 (9.8)

Source: Table 14.1.2

The screen failure rate was lower than anticipated, resulting in a total of 70, rather than 40, eligible subjects.

Charts were obtained from tertiary referral centres and so the geographic location of the centre may not necessarily correspond to the country of origin (or current country of residence) of the subject.

Due to the retrospective nature of this study, not all charts contained the same information. Based on the extent of the available data, the primary parameters analysed included visual acuity testing, Goldmann kinetic visual fields testing and optical coherence tomography.

Subject demographics are summarized in the following table:

Table 7 Demographic Summary

Parameter/Category/Statistic	Eligible (N = 70)	Ineligible (N = 32)	Total (N = 102)
Age (Year)*			
Mean (SD)	15 (11.8)	15 (18.3)	15 (14.9)
Median (IQR)	9 (3,18)	9 (3, 35.5)	9 (3, 24)
Min, Max	1, 43	1, 61	1, 61
Gender, n (%)			
Female	42 (60.0)	21 (65.6)	63 (61.8)
Male	28 (40.0)	11 (34.4)	39 (38.2)
Race, n (%)			
White	47 (67.1)	23 (71.9)	70 (68.6)
Asian	2 (2.9)	1 (3.1)	3 (2.9)
Black or African American	14 (20.0)	3 (9.4)	17 (16.7)
Other	1 (1.4)	2 (6.3)	3 (2.9)
Unknown	6 (8.6)	3 (9.4)	9 (8.8)
Ethnicity, n (%)			
Not Hispanic or Latino	58 (82.9)	22 (68.8)	80 (78.4)
Hispanic or Latino	9 (12.9)	6 (18.8)	15 (14.7)
Unknown	3 (4.3)	4 (12.5)	7 (6.9)

*Age is approximate since only birth years are available.
Source data: Table 14.1.1

Clinical history

General clinical history

Subject charts were collected from tertiary referral centres for inherited retinal disease and, in most cases, there was limited medical and/or surgical history available from the eligible charts.

Eye history

From the data available in the study charts, it did not appear that subjects were reliably or consistently queried at every visit regarding the presence or absence of orientation/mobility issues, use of low vision aids, nyctalopia, or photophobia. Therefore, it is not possible to draw definitive conclusions regarding the prevalence of these conditions in this study population.

For purposes of standardization, an attempt was made to classify the verbatim comments into broad categories describing function, as summarised:

Table 8 Ocular History at the Initial Visit

	Present n (%)	Absent or Not Noted n (%)	Total n
Orientation/Mobility Issues	52 (74.3%)	18 (25.7%)	70
Use of Low Vision Aids	56 (80.0%)	14 (20.0%)	70
Poor Night Vision	38 (54.3%)	32 (45.7%)	70
Photophobia	62 (88.6%)	8 (11.4%)	70

Source data: Westat Table 14.1.5; Listing 16.2.6

For a few subject charts with multiple visits over time, there was a clear progression of worsening vision, decreasing visual fields, and increasing reliance on visual aids, providing evidence of the decline in the ability to function independently as retinal degeneration continues and visual function is increasingly compromised.

Clinical diagnosis

A total of 76 clinical diagnoses were reported in the charts of the 70 subjects, with some subjects having more than one diagnosis at the time of the initial visit. In addition, subjects may have received one clinical diagnosis early on, which was subsequently changed over time as more information (usually genetic testing results) became available.

Among the 76 clinical diagnoses at the time of the first reported visit, 42 (55.3%) were LCA, 6 (7.9%) were RP, 5 (6.6%) were tapetal retinal dystrophy, 5 (6.6%) were SECORD, and 4 (5.3%) were EOSRD. 3 subjects each had a clinical diagnosis of “low vision” or “tapetal retinal dystrophy, Leber type”, while 2 subjects each had a clinical diagnosis of “RPE65-related LCA” and “cone rod dystrophy”. There were 12 subjects who had other unique clinical diagnoses. In total, there were 21 distinct clinical diagnoses assigned to this study population at the time of the initial visit.

There were 31 subjects who had more than one clinical diagnosis over the course of their visits. The average number of clinical diagnoses for this study population is 3, with a minimum of 1 and maximum of 7. There were 9 subjects who received a diagnosis of both LCA and RP over the course of their visits.

The age at clinical diagnosis was obtained from the 70 subject charts; for 48 charts (68.6%), subjects were younger than 18 years of age at the time of the recorded clinical diagnosis. 17 other subjects had the presence of symptoms noted at ages under 18.

Genetic diagnosis

All eligible subject charts had confirmation of autosomal recessive RPE65 mutation(s).

A number of mutations known to be associated with LCA, SECORD, and RP were observed. A total of 56 unique RPE65 mutations were observed in this study population, with 27 individuals (38.6%; 9 were homozygous) having at least one mutation known to be associated with LCA, 37 individuals (52.9 %; 7 were homozygous) having at least one mutation associated with SECORD, or RP, and 18

individuals (25.7%; 9 were homozygous) with other mutations not previously described in the context of any of these clinical diagnoses.

Data

Visual acuity

The method of visual acuity assessment obtained from the charts ranged from preferential gaze using Teller cards in pre-verbal children, to Allen Cards in older children, to Snellen acuity charts in adults. For purposes of standardization, all visual acuity assessments from the primary source were converted to decimals and then to LogMAR values using the following formula of Holladay (1997):

LogMAR= -Log (Decimal Acuity)

For the majority of available visual acuity assessments, each eye was measured separately; bilateral VA assessments were more limited. For purposes of this analysis, VA results are presented for the right eye and left eye, separately, using standardized LogMAR units. When available, best-corrected VA (BCVA) was used, as this is the standard and customary method of collecting VA assessments; however, there were many subject charts where BCVA was not clearly specified.

Data were collected from each subject over time at different ages, and longitudinal analyses for the effect of age on VA, using both Holladay and Lange scales for off-chart measurements, were performed. Data obtained from subjects between the ages of 0-3 were excluded due to the difficulty in obtaining reliable VA assessments in very young children.

There were a total of 309 measurements for the left eye and 331 measurements for the right eye collected from 68 subjects. Each subject had a varying number of measurements.

Table 9 Visual Acuity by Age Group (Left Eye)

Age (years)	N[a]	Holladay		Lange	
		Mean ± SD	Median (Range)	Mean ± SD	Median (Range)
4-5	27	0.80 ± 0.43	0.9 (-0.1 - 2.0)	0.80 ± 0.43	0.9 (-0.1 - 2.0)
6-7	45	0.84 ± 0.36	0.8 (0.2 - 2.4)	0.84 ± 0.36	0.8 (0.2 - 2.4)
8-9	40	0.82 ± 0.30	0.7 (0.3 - 1.5)	0.82 ± 0.30	0.7 (0.3 - 1.5)
10-11	32	0.84 ± 0.34	0.8 (0.4 - 1.8)	0.84 ± 0.34	0.8 (0.4 - 1.8)
12-13	20	0.98 ± 0.41	1.0 (0.1 - 1.8)	0.98 ± 0.41	1.0 (0.1 - 1.8)
14-15	19	0.97 ± 0.42	0.8 (0.0 - 1.6)	0.97 ± 0.42	0.8 (0.0 - 1.6)
16-17	19	1.09 ± 0.51	1.3 (0.1 - 2.0)	1.09 ± 0.51	1.3 (0.1 - 2.0)
18-19	18	1.09 ± 0.91	0.8 (0.1 - 4.0)	0.99 ± 0.64	0.8 (0.1 - 2.6)
20-21	22	1.13 ± 0.45	1.2 (0.1 - 2.0)	1.13 ± 0.45	1.2 (0.1 - 2.0)
22-23	12	1.43 ± 0.90	1.3 (0.7 - 4.0)	1.31 ± 0.56	1.3 (0.7 - 2.6)
24-25	7	1.45 ± 1.18	0.8 (0.7 - 4.0)	1.25 ± 0.70	0.8 (0.7 - 2.6)
26-27	11	2.30 ± 1.18	1.8 (0.9 - 4.0)	1.88 ± 0.60	1.8 (0.9 - 2.6)
28-29	7	2.05 ± 1.39	1.4 (0.9 - 4.0)	1.65 ± 0.76	1.4 (0.9 - 2.6)
30-31	9	1.20 ± 0.46	1.3 (0.5 - 1.8)	1.20 ± 0.46	1.3 (0.5 - 1.8)
32-33	11	1.92 ± 1.08	1.6 (0.8 - 4.0)	1.67 ± 0.57	1.6 (0.8 - 2.6)
34-46	10	2.94 ± 1.31	3.5 (1.0 - 4.0)	2.10 ± 0.68	2.4 (1.0 - 2.6)

[a] N denotes the number of VA measurements available for subjects within the specified age grouping, not the number of subjects.

Source: Table 1A, Table 2A Natural History Visual Acuity Statistical Analysis Report (04-Nov-2016)

Table 10 Visual Acuity by Age Group (Right Eye)

Age (years)	N[a]	Holladay		Lange	
		Mean ± SD	Median (Range)	Mean ± SD	Median (Range)
4-5	39	0.80 ± 0.41	0.8 (-0.1 - 1.7)	0.80 ± 0.41	0.8 (-0.1 - 1.7)
6-7	51	0.83 ± 0.30	0.9 (0.2 - 1.8)	0.83 ± 0.30	0.9 (0.2 - 1.8)
8-9	41	0.84 ± 0.37	0.7 (0.2 - 1.5)	0.84 ± 0.37	0.7 (0.2 - 1.5)
10-11	33	0.88 ± 0.37	0.8 (0.3 - 1.8)	0.88 ± 0.37	0.8 (0.3 - 1.8)
12-13	20	0.94 ± 0.41	0.9 (0.1 - 1.8)	0.94 ± 0.41	0.9 (0.1 - 1.8)
14-15	20	0.92 ± 0.37	0.8 (0.1 - 1.6)	0.92 ± 0.37	0.8 (0.1 - 1.6)
16-17	18	1.04 ± 0.43	1.1 (0.4 - 1.8)	1.04 ± 0.43	1.1 (0.4 - 1.8)
18-19	20	1.12 ± 0.63	1.1 (0.2 - 2.5)	1.09 ± 0.55	1.1 (0.2 - 2.2)
20-21	22	1.26 ± 0.44	1.3 (0.3 - 2.0)	1.26 ± 0.44	1.3 (0.3 - 2.0)
22-23	12	1.46 ± 0.94	1.3 (0.2 - 4.0)	1.34 ± 0.64	1.3 (0.2 - 2.6)
24-25	7	1.27 ± 1.29	1.0 (0.2 - 4.0)	1.07 ± 0.82	1.0 (0.2 - 2.6)
26-27	11	1.67 ± 0.69	1.8 (0.7 - 3.0)	1.57 ± 0.53	1.8 (0.7 - 2.3)
28-29	7	1.87 ± 1.24	1.4 (0.7 - 4.0)	1.57 ± 0.76	1.4 (0.7 - 2.6)
30-31	9	1.37 ± 0.69	1.3 (0.6 - 2.6)	1.32 ± 0.60	1.3 (0.6 - 2.3)
32-33	11	1.91 ± 0.88	1.8 (0.8 - 4.0)	1.72 ± 0.53	1.8 (0.8 - 2.6)
34-46	10	3.17 ± 1.30	3.5 (1.0 - 5.0)	2.22 ± 0.63	2.4 (1.0 - 2.9)

[a] N denotes the number of VA measurements available for subjects within the specified age grouping, not the number of subjects.
Source: Table 1B, Table 2B Natural History Visual Acuity Statistical Analysis Report (04-Nov-2016)

Visual field data

Visual field assessments were collected primarily using manual Goldmann kinetic perimetry. Cumulative visual fields were calculated across 24 meridians for each stimulus tested (III4e, V4e, and other test stimuli [I3e, I4e, II4e, IV4e]).

For each stimulus tested, the outcome measure is the sum total meridian degrees (or sum total degrees); higher sum total degrees indicate a greater area of functional and light sensitive retina, corresponding to a greater field of vision for the subject.
The sum total meridian degrees represents a summation of the measure of degrees from central fixation to the point of the isopter intersection for each of the 24 meridians. Using this approach, the maximal visual field is approximately 1400-1800 sum total meridian degrees in individuals without visual impairment.

For purposes of standardization, kinetic visual fields obtained using automated Octopus technology (11 subjects) were excluded from this analysis, as were computerized static Humphrey visual fields (13 subjects), since the available data were not sufficient for analysis.

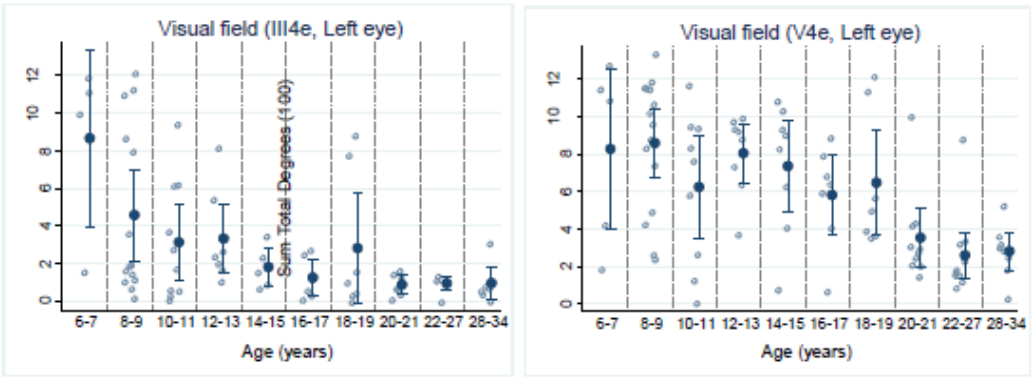
Data were collected from each subject over time at different ages, and were analyzed for the right eye and left eye, separately. Longitudinal analyses for the effect of age on visual field by test stimulus type

(III4e and V4e only) were conducted. Goldmann visual fields using other test stimulus types (I3e, I4e, II4e, IV4e) were excluded from this analysis.

Subjects who had only one measurement for each eye were excluded. A total of 161 measurements for the left eye and 160 measurements for the right eye were collected from 27 subjects (with repeated III4e and V4e measurements). Each subject had a varying number of measurements. If there were multiple measurements obtained for the same eye and same test stimulus type on the same date, the average of the measurements was used.

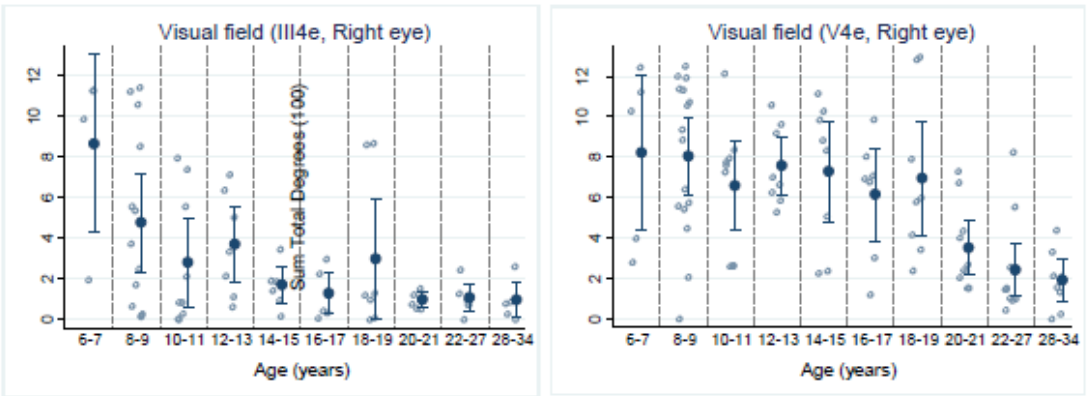
Data are summarised in the figures below:

Figure 11 Visual Fields by Age and Test Type (Left Eye)



Source: Table 7A and Table 7B, Natural History Visual Field Statistical Analysis Report (04-Nov-2016)

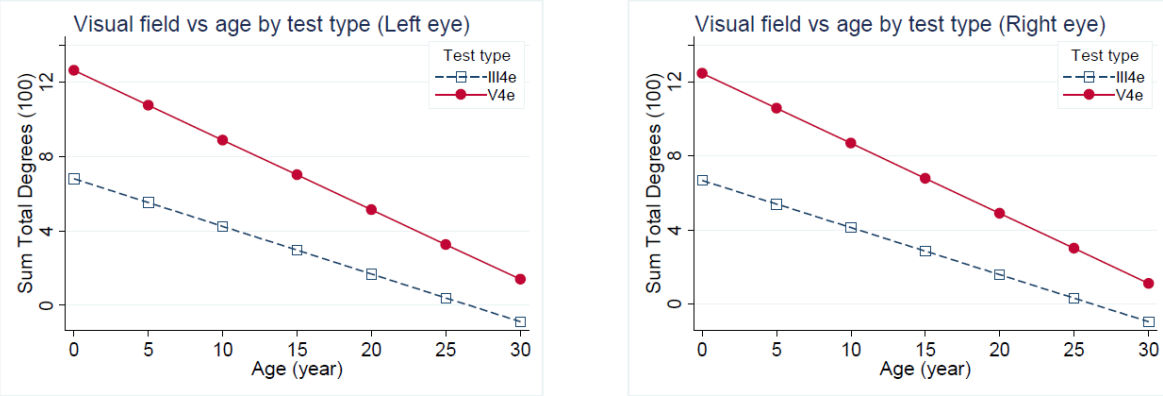
Figure 12 Visual Fields by Age and Test Type (Right Eye)



Source: Table 8A and Table 8B, Natural History Visual Field Statistical Analysis Report (04-Nov-2016)

On average, in this cohort, a 1 year increase in age decreased the III4e visual field by approximately 25 sum total degrees in each eye; the less discriminatory V4e visual field, which tended to be larger than the visual field as measured by III4e, decreased by approximately 37 sum total degrees, in each eye.

Figure 13 Mean Goldman Visual Fields – by Age and Stimulus Type (Left and Right Eyes)



2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The company conducted a natural history study (code RPE65 NHx) of 32 subjects with a diagnosis of Leber's congenital amaurosis type 2. Visual acuity in these subjects was shown to progressively deteriorate from birth; there was an acceleration of deterioration in visual acuity after the late teenage years. The areas of subjects' visual fields were also shown to decline progressively from a young age. Thickness of the retinal layer of the eye, however, did not change up to years mid-30s.

The company has submitted clinical intervention studies 101 and 102; these were open-label, uncontrolled, non-randomised phase I studies in subjects with Leber's congenital amaurosis type 2. Study 101 enrolled 12 subjects (7 male, 5 female) ages 8 to 44yrs with Leber' s congenital amaurosis and visual acuity ≤ 20/160. Study drug was administered to one eye (direct to the sub-retinal space) at either low dose (1.5E10 vg), medium dose (4.8E10 vg) or high dose (1.5E11 vg). 11 of these subjects later went forwards to study 102 to have the study drug administered to the second eye at dose 1.5E11 vector genomes (vg). Efficacy was measured by score achieved on an in-house mobility assessment tool (under development at this stage). The results of studies 101 and 102 encouraged the company to develop its in-house mobility assessment tool and to go forward to study 301/2 using the high dose of study drug i.e. 1.5E11 vg AAV2-hRPE65v2 (per eye) delivered in a total sub-retinal volume of 300µL. The mobility assessment tool was further developed for use in studies 301/302.

The final version of the mobility assessment tool as used in study 301/302 is a 7 foot by 12 foot obstacle course with 15 obstacles of varying size, shape and colour; 1 of 12 described routes may be chosen; ambient light may be reduced from 400 lux to 1 lux to conduct the study; subjects are marked according to time taken to go from start to finish and by success in avoiding or navigating obstacles in the path. 3 errors in navigation were permitted per run. Penalty points were added for infringements. A pass time score of <180 seconds was chosen. Subjects were marked as 'pass' or 'fail' based on the accuracy and time scores. The tool returns an ordinal result.

A validation exercise for the tool has been submitted by the company comparing scores achieved by healthy subjects with subjects with a variety of eye diseases (not only Leber's congenital amaurosis).

The mobility tool is considered to display notable deficiencies. Thus, a pass time score of <180 seconds leads to a broad 'ceiling effect' that will impair the ability of the tool to detect change over time. Further, subjects in the control phase of study 301/302 demonstrate ±1 change in score over 1 year and so change would need to exceed this in order to be considered clinically significant.

The efficacy of voretigene neparvovec (AAV2-hRPE65v2) in the treatment of LCA patients with RPE65 mutations was evaluated in pivotal study 301/302.

- Study 301 was an open label, randomised, multi-centre, parallel group study to evaluate the efficacy and safety of AAV2- hRPE65v2 to subjects with Leber congenital amaurosis due to RPE65 mutations. Intervention subjects received sequential, bilateral, subretinal administration of AAV2-hRPE65v2 while Control subjects remained un-injected for one year.

- After the first year of un-injected follow up, Control subjects were eligible to cross over to injection with AAV2-hRPE65v2 (study 302).

A single pivotal study was deemed to be acceptable considering the rarity and the progressive nature of the pursued indication. The clinical program as well as the design and outcomes of the Study 301 were discussed during a protocol assistance in July 2013 (EMA/CHMP/SAWP/429802/2013) and a follow-up protocol assistance in December 2015 (EMA/CHMP/SAWP/819724/2015).

Study 301/302 recruited patients aged 3 years old or older, with LCA genetically confirmed to be due of RPE65 mutations with documented sufficient viable retinal cells were eligible for the study. Patients were selected according to the visual function deterioration (visual acuity 20/60 or worse, or visual field less than 20 degrees in any meridian), a relevant clinical feature of the disease, and the ability to perform a mobility testing within the luminance range evaluated in the study. The study was conducted in two centres in USA (Children's Hospital of Philadelphia and University of Iowa). A total of 5 patients (16%) were from EU countries.

A total of 36 patients were screened and 31 out of 36 were randomized (ITT population). A total of 29 patients (20 in the Intervention group and 9 in the Control group) formed the mITT population. The limited number of patients is acceptable given the rarity of the disease.

Overall 13 (42%) males and 18 (58%) females were included. The mean age at randomization was 15.1 years, with patients from 4 to 44 years. Overall 42% patients were younger than 10 years and 58% were equal or older than 10 years. Subjects of less than 3 years of age were not considered for this study. The main limitation in children less than three years of age comes from the risks associated with the surgical administration procedure

All patients presented nystagmus and retina abnormalities at entry. Strabismus was reported in eight (38%) intervention subjects and five (50%) control subjects. At Baseline visual acuity (averaged across both eyes) was severely impaired (mean logMAR 1.18 in the intervention group and 1.29 in the control group), and all subjects recruited in the study presented low vision (≥ 0.6 LogMAR, equivalent to 20/80, or greater).

Molecular diagnosis confirmed the mutation in the RPE65 gene and a wide range of mutations were reported. Different point mutations cause different deficiencies in RPE65 function and may lead to the heterogeneity observed in disease phenotypes.

Patients assigned to active group received 1.5E11 vg in each eye (non-simultaneously) administered by subretinal injection. The second eye was treated 6-18 days after the first one. In order to reduce

the potential for an intraocular inflammation a perioperative course of corticosteroids was given (1 mg/kg/day prednisone up to 40 mg/day for seven days and then tapered).

No formal dose finding study was performed. The dose finally chosen dose (1.5E11 vg in a total subretinal volume of 300 µL per eye) was the highest dose tested in Phase I. Surgery was performed under general anaesthesia with the use of a standard three-port pars plana vitrectomy. The treatment is administered by means of a subretinal cannula to the subretinal space involving up to one third of the total retinal area, including the macula. Relevant aspects in relation to the product administration are the selection of the retinal area to be injected by OCT (where more viable retinal cells are exposed to the vector) and the avoidance the immediate vicinity of the central macula (within 2 mm from the foveal centre) in order to reduce potential macular complications.

Efficacy data

The company has presented results by group analysis and by means of bar charts to show individual response.

Progress of subjects was monitored by measuring the score obtained on the mobility assessment tool (binocular mode) and by estimation of full field light sensitivity and visual acuity at baseline and then obtaining change scores at day 30, day 90, day 180 and years 1, 2 and 3 after exposure. The company intends to follow subjects for 15 years after exposure to study drug.

The primary endpoint for studies 301/302 was change in score [from baseline to 1 year after exposure to study drug] using the company's in-house mobility tool. Subjects used binocular vision to carry out the test. The tool returned ordinal scores between -1 and +6 (pass at 1 lux). At baseline, subjects achieved pass marks on the mobility test at between 4 and 400 ambient lux i.e. there was a wide range of competence.

At 1 year, the difference (95% CI) between intervention and control [based on the ITT population] was +1.6 (0.72, 2.41), $p<0.001$ i.e. subjects exposed to study drug were better able to navigate the course with binocular vision. The improved ability to navigate the test course was sustained over 3 years.

Clinical efficacy has not been demonstrated in all subjects. The company was requested to discuss methods to identify those who will likely respond. No predictors of response or non-response have been identified from the data, including age, gender, baseline status of VA or VF, or specific genetic mutation. Only the presence of a sufficient number of viable cells appears the determining feature for the effect. It is accepted that there was not a suitable functional assessment of retinal viability and that the use of optical tomography, as described by the company, to measure retinal thickness as a guide to viability of retinal cells was probably the only option available.

The primary endpoint was supported by the main secondary endpoints.

Thus, for the secondary endpoint of change in mobility test score at 1 year using monocular vision with the first assigned eye only, the difference (95% CI) between intervention and control [based on the ITT population] was +1.7 (0.89, 2.52) i.e. subjects exposed to study drug were better able to navigate the course with monocular vision.

For the secondary endpoint of change in change in full-field light sensitivity at 1 year for the first assigned eye only, the difference (95% CI) between intervention and control [based on the ITT population] was -2.33 (-3.44, -1.22), $p<0.001$.

For the secondary endpoint of change in change in full-field light sensitivity at 1 year for the second assigned eye only, the difference (95% CI) between intervention and control [based on the ITT population] was -1.89 (-3.03, -0.75), p<002.

The full-field light sensitivity results demonstrate improved retinal sensitivity to light consequent to exposure to study drug.

For visual acuity, at one year after exposure to voretigene neparvovec, improvement in visual acuity of at least 0.3 LogMAR occurred in 11 (55%) of the first-treated eyes and 4 (20%) of the second-treated eyes; no one in the control group displayed such an improvement of visual acuity in either the first or second eye.

Patients treated with voretigene neparvovec showed improvement in kinetic visual field area, with a decrease in the visual field area in the untreated group. This difference during the study was statistically significant for III4e but not for V4e target. It has been attributed to the reduced number of patients performing V4e target compared to III4e target.

Improvement in visual function was noted within the first month of the study followed by an apparent stabilisation until the end of the observation period without further changes. A consistent response was also shown in the sensitivity analyses (mITT, PP) conducted.

Additional expert consultation

Question 1

Please discuss the differences and similarities of LCA type 2 and retinitis pigmentosa (when associated with biallelic mutations of the RPE65 gene) at the time of study conduct and according to current understanding.

Given the assertion from the Company that the understanding of the disease has evolved recently, please comment on the representativeness of the "studied population" to "patients with vision loss due to Leber congenital amaurosis or retinitis pigmentosa inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells."

Opinion of the experts

The experts commented that the diagnostic terms LCA2 and RP20 are imprecise, misleading and thus not ideal to be used in this context. For example, some publications classify RP 20 as a mild form of LCA2. Indeed, LCA2 and RP20 represent a phenotypic continuum of the same disease. The experts agreed that the preferred approach would be to use the term "retinal dystrophy caused by biallelic RPE65 mutations", in order to describe the underlying biology of the disease.

The nature and sequence of diagnostic tests in the EU varies from country to country and between specialist centres. The timing of genetic testing depends, among other things, on the age of onset and clinical presentation. Genetic testing is not currently available to patients in parts of the EU.

The experts were of the opinion that in order to avoid the situation where patients with retinitis pigmentosa associated with biallelic mutations of the RPE65 gene do not receive this treatment, an option would be to reclassify them as LCA2 by their physicians, if Luxturna indication was limited to LCA2 only. However, the experts agreed that an indication given for any "retinal dystrophy caused by biallelic RPE65 mutation" would be a more sensible strategy.

Question 2

Does the expert group consider that the number of viable retinal cells measured by (OCT) is deemed a reliable measure in order to identify candidates to be treated?

In this context please discuss if the following criteria are adequate to determine the presence of 'sufficient viable retinal cells as determined by non-invasive means such as computerised tomography (OCT) and / or ophthalmoscopy.

Must have either:

- *an area of retina within the posterior pole of >100µm thickness shown on OCT*
- *≥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 III4e isopter or equivalent*

Are there more appropriate methods to determine viability of retinal cells?

Opinion of the experts

The experts' view on the criteria proposed in the current labelling is that these are not optimal. It was suggested that the treating physician is best placed to determine if the patient has sufficient viable retinal cells to justify therapy.

Experienced ophthalmologists in specialist centres would be most suitable to have an informed discussion with the patients about the specific pertinence of the treatment. In addition, as technology is moving on rapidly, the experts were reluctant to include specific tests and cut-off values in the labelling.

It was stated that determining whether a patient should be treated with Luxturna should involve assessment of both structure and function of the retina.

OCT could be used to assess structure but should be focused on assessment of outer retinal structures (outer nuclear layer, and inner segments), rather than total retinal thickness. Reference to posterior pole could also be removed. Full field stimulus could be used as a functional test. Electrophysiological tests were suggested by some experts but as they were thought not useful by other experts (floor effect of the signal), this proposal was not endorsed by the wider group.

It was also noted that it may be difficult to perform OCT imaging in young children without general anaesthesia and a functional test could not be feasible in young children. However, such young patients are highly likely to have sufficient viable cells and a functional test would therefore not be necessary in these patients.

Intra -operative OCT was also suggested as part of treatment administration procedure.

Question 3

Please discuss if it possible to decide on a "window of opportunity" for treatment based on age of patient, rate of progression of disease and the different phenotypes of Leber's congenital amaurosis and retinitis pigmentosa (when associated with mutations of the RPE65 gene) taking also into account that currently the durability of the Luxturna effect is not known and the possibility to repeat the administration has not been studied. Are there other factors that may be taken into account?

Opinion of the experts

The experts advised that window of opportunity is better defined by disease severity, rather than age. The presence of existing viable retinal cells should be the key factor to identify if a patient is likely to benefit from treatment. The decision to treat should be based on individual risk/benefit assessment, taking into account possible safety concerns related to surgical procedure and patient's preferences. It

was noted that all patients in clinical trials had some degree of vision loss before the intervention (i.e. BCVA < 20/60) but this would not have to be a prerequisite for treatment (as evidenced by FDA label).

As the RPE cell proliferation is ongoing until 12 months of age, efficacy of earlier intervention may be limited (dilution of episomal transgene copies during cell division). There are also technical limitations of surgery in children younger than 3 years of age, although this needs to be balanced with the fact that earlier treatment may aid development of visual cortex. The absence of safety data in patients younger than four years was identified as a caveat for recommending treatment, despite the fact that it was recognised that children younger than 4 years could benefit based on individual assessment.

2.5.4. Conclusions on the clinical efficacy

The efficacy of voretigene neparvovec has been evaluated in LCA2 patients with poor vision under low light conditions. After 1 year, the ability of patients to navigate a stylised maze (the mobility test tool) had improved. The primary endpoint of the study 301 was met. This effect has been maintained up to at least 3 years (although this is a limited follow-up period, the company intends to follow patients for 15yrs total). Results of secondary endpoints are supportive towards the primary endpoint.

The CHMP endorses the CAT conclusion on clinical efficacy as described above.

2.6. Clinical safety

Patient exposure

At the time of the 05-May-2017 cut-off date, the clinical datasets consisted of at least seven years of cumulative Study 101 and Study 102 data, with at least four years of data following administration to the second eye in Study 102. For Phase 3 (Study 301 / 302), the datasets consist of at least three years of data for the Original Intervention subjects and at least two years of data for the Control / Intervention subjects.

The clinical development program included 43 subjects across the Phase 1 (n = 12) and Phase 3 (n = 31) studies, with 41 (95%) subjects receiving AAV2-hRPE65v2 (bilateral injection, n = 40 [98%]; unilateral injection, n = 1 [2%]).

The following table presents the exposure by subject and by eye for each study:

Table 11 Vector Exposure. Subject Exposure to AAV2-hRPE65v2

Study	Dose cohorts Number of subjects			Total number of eyes exposed	Total number of subjects exposed
Subretinal volume (microliters)	150 µL	150 µL	300 µL		
Dose (vector genomes)	1.5E10 vg	4.8E10 vg	1.5E11 vg		
Study 101 (First Eye)	3	6	3	12	12
Study 102 (Second Eye)	-	-	11[a]	11[a]	
Study 301 (Both Eyes) Original Intervention	-	-	20[b]	40	29
Study 302 (Both Eyes) Control / Intervention	-	-	9[b]	18	
Total				81	41

[a] One subject (CH-13, high dose group) was not eligible for Study 102; 2nd eye did not receive AAV2-hRPE65v2.

[b] Two subjects were discontinued before administration of AAV2-hRPE65v2; one from the Intervention group and one from the Control group

Source data: Study 101 CSR, Listing 16.2.8.19; Study 102 CSR, Listing 16.2.8.19; Study 301 CSR Addendum 2016, Table 14.1.1.7.

81 eyes in 41 subjects were exposed to the vector at dosages described in the above table.

14 (34%) subjects were from outside of the U.S. (Europe, Canada, and Mexico) including 12 (29%) subjects from Europe (Italy, Belgium, and Netherlands).

In Study 102, the previously un-injected contralateral eye of each enrolled subject from study 101 received 1.5E11 vg AAV2-hRPE65v2 in a total sub-retinal volume of 300 µL.

The mean duration between first and second injections in study 301/3021 was 8.4 ± 2.3 days (range 7 to 14 days). The 6 to 18 day interval between administrations was used in Phase 3 to afford an opportunity for identification of early-emergent potential surgical complications prior to a subject undergoing the second procedure, and to reduce the risk of a deleterious immune response by carrying out the two administration procedures in a near simultaneous fashion, rather than a more widely spaced interval that could facilitate a prime boost response.

Demographics of subjects

The demographic characteristics of all subjects who were exposed to AAV2-hRPE65v2 are presented in the following table:

Table 12 Demographics Characteristics (All Subjects Receiving AAV2-hRPE65v2)

Variable	101[a] (N = 12)	102[a] (N = 11)	301 / 302			Overall Total Phase 1 + Phase 3 (N = 41)
			Intervention (N = 20)	Control (N = 9)	Total (N = 29)	
Age[b]	[b]	[c]	[b]	[b]	[b]	[b]
Mean (SD) (years)	20.8 (11.2)	22.8 (10.3)	14.6 (12.0)	15.2 (8.3)	14.8 (10.8)	16.6 (11.1)
Range (years)	8, 44	11, 46	4, 44	5, 29	4, 44	4, 46
Pediatrics (< 18 years), N (%)	5 (42%)	4 (36%)[d]	15 (75%)	5 (50%)	20 (69%)	25 (61%)
Adults (≥ 18 years), N (%)	7 (58%)	7 (64%)[d]	5 (25%)	4 (44%)	9 (31%)	16 (39%)
Gender, N (%)						
Male	7 (58%)	6 (55%)	8 (40%)	3 (33%)	11 (38%)	18 (44%)
Female	5 (42%)	5 (46%)	12 (60%)	6 (67%)	18 (62%)	23 (56%)
Race, N (%)						
White	11 (92%)	10 (91%)	14 (70%)	6 (67%)	20 (69%)	31 (76%)
Asian	1 (8%)	1 (9%)	2 (10%)	2 (22%)	4 (14%)	5 (12%)
American Indian or Alaska Native	0	0	2 (10%)	1 (11%)	3 (10%)	3 (7%)
Black or African American	0	0	2 (10%)	0	2 (7%)	2 (5%)
Ethnicity, N (%)						
Hispanic	0	0	5 (25%)	1 (11%)	6 (21%)	6 (15%)
Non-Hispanic	12 (100%)	11 (100%)	15 (75%)	8 (89%)	23(79%)	35 (85%)

[a] The same subjects participated in Studies 101 and 102.
[b] Age at first injection; the age at first eye injection (Study 101) was used for the overall total.
[c] Age at second injection (Study 102 only).
[d] Subject NP-04 was 17 years old at 1st injection and 21 years old at 2nd injection, hence classified as pediatric in Study 101 and as adult in Study 102.

Source data: Module 5.3.5.3, Study 101, Table 14.1.2; Module 5.3.5.3, Study 102, Table 14.1.2; Study 301 CSR Addendum 2016, Table 14.1.1.3

Adverse events

All subjects had at least one treatment emergent adverse event. In Phase 1 (Studies 101 and 102), the most frequent AEs by SOC were Infections and Infestations (n = 11 subjects, 92%), Eye Disorders (n = 10 subjects, 83%), and General Disorders and Administration Site Conditions (n = 8 subjects, 67%). At the PT level, the most frequent events were conjunctival hyperaemia (n = 8 subjects, 67%), pyrexia (n = 7 subjects, 58%), and leukocytosis (n = 6 subjects, 50%). The majority of the TEAEs in the Phase 1 subjects were mild.

The most frequent AEs by SOC for all 29 Phase 3 subjects through 05-May-2017 were Eye Disorders (n = 17 subjects, 59%), Gastrointestinal Disorders (n = 17 subjects, 59%) and Nervous System Disorders (n = 16 subjects, 55%). At the PT level, the most frequent events were headache (n = 13 subjects, 45%), leukocytosis (n = 11 subjects, 38%), nausea (n = 10 subjects, 35%), and vomiting (n = 10 subjects, 35%). The majority of the TEAEs were mild and not related to the vector.

Adverse Events by Relationship to the Vector

3 TEAEs of retinal deposit (verbatim subretinal precipitate), considered probably related to AAV2-hRPE65v2 but not to the administration procedure, were reported in three subjects. Following subretinal administration of AAV2-hRPE65v2, a semi-circular white line (open superiorly) was observed in one eye each of three subjects; this finding was not observed in the contralateral eye of any of these subjects, who each underwent bilateral administration of AAV2-hRPE65v2 within 18 days per protocol. The observed line (retinal deposit) was not in the area of the subretinal bleb / injection site, but rather was inferior to the initial injection bleb, and well below the temporal vascular arcade. The TEAEs of retinal deposit were a transient, asymptomatic fundoscopic finding with no observed clinical correlate. All of them resolved by 8 weeks.

Adverse Events by Relationship to the Administration Procedure or Vector

In Study 301, a total of 13 (65%) subjects in the Intervention group had at least one TEAE that was assessed as related to the administration procedure. The majority were Eye Disorders (n = 8 [40%] subjects), with cataract (n = 4 [20%] subjects through data cut-off) as the most frequently reported PT.

In Study 302, a total of six Control / Intervention subjects had at least one TEAE that was assessed as related to the administration procedure. The majority were Eye Disorders (n = 6 [67%] subjects). Nausea was reported in two subjects; all other administration procedure-related events were reported in only one subject.

In Study 101, ten (83%) subjects had at least one TEAE that was related to the administration procedure. The majority of these TEAEs were Eye Disorders (n = 9 [75%] subjects), with conjunctival hyperaemia (n = 8 [67%] subjects) as the most frequently reported PT.

In Study 102, seven (64%) subjects had at least one TEAE that was related to the administration procedure. The majority were Eye Disorders (n = 7 [64%] subjects), with dellen (n = 3 [27%] subjects) as the most frequently reported PT.

In the addendum with a revised cut-off date 05 May 2017, the company reports on 9 new events. five events were considered related to the administration procedure, including one Phase 1 event (cataract) and four Phase 3 events (cataract and eyelid ptosis).

Related adverse events are summarised in the following table:

Table 13 All Adverse Reactions Related to the Vector or to the Administration Procedures – All Studies – 120-Day Safety Update Data Cut-Off 05-May-2017

	Phase 1						Phase 3						Total	
	Study 101 (N = 12 Subjects; (N = 12 Eyes)		Study 102 (N = 11 Subjects; (N = 11 Eyes)		Phase 1 Total (N = 12 Subjects; (N = 23 Eyes)		Original Intervention (N = 20 Subjects; N = 40 Eyes)		Control / Intervention (N = 9 Subjects; N = 18 Eyes)		Phase 3 Total (N = 29 Subjects; N = 58 Eyes)		Phase 1 + Phase 3 (N = 41 Subjects; N =81 Eyes)	
MedDRA SOC / PT	Subjects n (%)	n Eyes	Subjects n (%)	n Eyes	Subjects n (%)	n Eyes	Subjects n (%)	n Eyes	Subjects n (%)	n Eyes	Subjects n (%)	n Eyes	Subjects n (%)	n Eyes
Eye Disorders	**9 (75%)**	**9**	**8 (73%)**	**10**	**9 (75%)**	**16**	**10 (50%)**	**16**	**6 (67%)**	**9**	**16 (55%)**	**25**	**25 (61%)**	**41**
Cataract	1 (8%)	1	3 (27%)	4	3 (25%)	5	4 (20%)	8	1 (11%)	2	5 (17%)	10	8 (20%)	15
Choroidal haemorrhage	0	0	0	0	0	0	0	0	1 (11%)	1	1 (3%)	1	1 (2%)	1
Conjunctival cyst	0	0	0	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)	1
Conjunctival hyperaemia[a]	8 (67%)	8	0	0	8 (67%)	8	0	0	1 (11%)	1	1 (3%)	1	9 (22%)	9
Dellen	0	0	3 (27%)	3	3 (25%)	3	0	0	0	0	0	0	3 (7%)	3
Eye disorder[b]	1 (8%)	1	0	0	1 (8%)	1	0	0	0	0	0	0	1 (2%)	1
Eye inflammation[c]	0	0	1 (9%)	1	1 (8%)	1	2 (10%)	4	0	0	2 (7%)	4	3 (7%)	5
Eye irritation	0	0	1 (9%)	1	1 (8%)	1	1 (5%)	1	0	0	1 (3%)	1	2 (5%)	2
Eye pain	0	0	1 (9%)	1	1 (8%)	1	0	0	1 (11%)	1	1 (3%)	1	2 (5%)	2
Eye swelling	0	0	0	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)	1
Eyelid ptosis	0	0	0	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)	1
Foreign body sensation in eyes	0	0	0	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)	1
Macular degeneration[d]	0	0	0	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)	1
Macular hole	1 (8%)	1	0	0	1 (8%)	1	1 (5%)	1	1 (11%)	1	2 (7%)	2	3 (7%)	3
Maculopathy[e]	0	0	1 (9%)	1	1 (8%)	1	1 (5%)	2	0	0	1 (3%)	2	2 (5%)	3
Retinal deposit[f]	0	0	0	0	0	0	0	0	3 (33%)*	3*	3 (10%)*	3*	3 (7%)*	3*
Retinal disorder[g]	0	0	0	0	0	0	0	0	1 (11%)	2	1 (3%)	2	1 (2%)	2
Retinal haemorrhage	0	0	0	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)	1
Retinal tear	1 (8%)	1	0	0	1 (8%)	1	2 (10%)	2	1 (11%)	1	3 (10%)	3	4 (10%)	4
Gastrointestinal Disorders														
Abdominal pain upper	0	NA	0	NA	0	NA	0	NA	1 (11%)	NA	1 (3%)	NA	1 (2%)	NA
Lip pain	0	NA	0	NA	0	NA	1 (5%)	NA	0	NA	1 (3%)	NA	1 (2%)	NA

	Phase 1						Phase 3						Total	
	Study 101 (N = 12 Subjects; (N = 12 Eyes)		Study 102 (N = 11 Subjects; (N = 11 Eyes)		Phase 1 Total (N = 12 Subjects; (N = 23 Eyes)		Original Intervention (N = 20 Subjects; N = 40 Eyes)		Control / Intervention (N = 9 Subjects; N = 18 Eyes)		Phase 3 Total (N = 29 Subjects; N = 58 Eyes)		Phase 1 + Phase 3 (N = 41 Subjects; N =81 Eyes)	
MedDRA SOC / PT	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**
Nausea	0	NA	0	NA	0	NA	1 (5%)	NA	2 (22%)	NA	3 (10%)	NA	3 (7%)	NA
Vomiting	0	NA	0	NA	0	NA	1 (5%)	NA	1 (11%)	NA	2 (7%)	NA	2 (5%)	NA
Injury, Poisoning & Procedural Complications														
Endotracheal intubation complication	1 (8%)	NA	0	NA	1 (8%)	NA	0	NA	0	NA	0	NA	1 (2%)	NA
Wound dehiscence[h]	0	0	0	0	0	0	0	0	1 (11%)	1	1 (3%)	1	1 (2%)	1
Investigations														
Electrocardiogram T wave inversion	0	NA	0	NA	0	NA	1 (5%)	NA	0	NA	1 (3%)	NA	1 (2%)	NA
Intraocular pressure increased	0	0	2 (18%)	2	2 (17%)	2	3 (15%)	4	1 (11%)	2	4 (14%)	6	6 (15%)	8
Nervous System Disorders														
Dizziness	0	NA	0	NA	0	NA	0	NA	1 (11%)	NA	1 (3%)	NA	1 (2%)	NA
Headache	0	NA	1 (9%)	NA	1 (8%)	NA	1 (5%)	NA	1 (11%)	NA	2 (7%)	NA	3 (7%)	NA
Psychiatric Disorders														
Anxiety	0	NA	0	NA	0	NA	0	NA	1 (11%)	NA	1 (3%)	NA	1 (2%)	NA
Skin & Subcutaneous Tissue Disorders														
Rash	0	NA	0	NA	0	NA	1 (5%)	NA	0	NA	1 (3%)	NA	1 (2%)	NA
Swelling face	0	NA	0	NA	0	NA	1 (5%)	NA	0	NA	1 (3%)	NA	1 (2%)	NA

	Phase 1						Phase 3						Total	
	Study 101 (N = 12 Subjects; (N = 12 Eyes)		Study 102 (N = 11 Subjects; (N = 11 Eyes)		Phase 1 Total (N = 12 Subjects; (N = 23 Eyes)		Original Intervention (N = 20 Subjects; N = 40 Eyes)		Control / Intervention (N = 9 Subjects; N = 18 Eyes)		Phase 3 Total (N = 29 Subjects; N = 58 Eyes)		Phase 1 + Phase 3 (N = 41 Subjects; N =81 Eyes)	
MedDRA SOC / PT	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**	**Subjects n (%)**	**n Eyes**

NA = not applicable. Values presented as number of subjects (% of subjects) and as number of eyes where applicable (ocular events).
*Related to the vector (AAV2-hRPE65v2)

[a] Includes verbatim terms of suture irritation and suture reaction.
[b] Verbatim term: foveal dehiscence
[c] Including one case of endophthalmitis (verbatim term: intraocular inflammation endophthalmitis)
[d] Verbatim term: macular thinning; follow-on event to a full-thickness macular hole (resolution without surgical intervention)
[e] Includes verbatim terms of epiretinal membranes and macular pucker.
[f] Verbatim term: subretinal precipitate
[g] Includes verbatim terms of foveal thinning and loss of foveal function.
[h] Verbatim term: suture dehiscence

Source data: Module 5.3.5.3, 120-Day Safety Update, Study 101, Listing 16.2.7.2; Module 5.3.5.3, 120-Day Safety Update, Study 102, Listing 16.2.7.2; Module 5.3.5.3, 120-Day Safety Update, Study 301, Listing 16.2.7.2 and Listing 16.2.7.3.

Adverse Events of Special Interest

Ocular TEAEs are considered events of special interest and are summarised in the following table:

Table 14 Summary of Ocular TEAEs – All Studies – Data Cut-Off 05-May-2017

	Phase 1			Phase 3						Total Phase 1 + Phase 3 (N = 41)
	Study 101 (N = 12)	Study 102 (N = 11)	Total Phase 1 (N = 12)	Original Intervention (N = 20 Subjects; N = 40 Eyes)		Control / Intervention (N = 9 Subjects; N = 18 Eyes)		Phase 3 Total (N = 29 Subjects; N = 58 Eyes)		
MedDRA SOC / PT	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)	n Eyes	Subjects n (%)	n Eyes	Subjects n (%)	n Eyes	Subjects n (%)
Any Ocular TEAE	**11 (92%)**	**9 (82%)**	**11 (92%)**	**12 (60%)**	**22**	**7 (78%)**	**12**	**19 (66%)**	**34**	**30 (73%)**
Eye Disorders	**10 (83%)**	**9 (82%)**	**10 (83%)**	**11 (55%)**	**19**	**6 (67%)**	**10**	**17 (59%)**	**29**	**27 (66%)**
Cataract	1 (8%)[a]	4 (36%)[a]	4 (33%)	4 (20%)	8	1 (11%)	2	5 (17%)	10	9 (22%)
Chalazion	0	1 (9%)	1 (8%)	0	0	0	0	0	0	1 (2%)
Choroidal haemorrhage	0	0	0	0	0	1 (11%)	1	1 (3%)	1	1 (2%)
Conjunctival cyst	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)
Conjunctival hyperaemia	8 (67%)	0	8 (67%)	0	0	1 (11%)	1	1 (3%)	1	9 (22%)
Conjunctivitis	1 (8%)	0	1 (8%)	0	0	0	0	0	0	1 (2%)
Dellen	0	3 (27%)	3 (25%)	0	0	0	0	0	0	3 (7%)
Diplopia	0	1 (9%)	1 (8%)	0	0	0	0	0	0	1 (2%)
Eye discharge	1 (8%)	0	1 (8%)	0	0	0	0	0	0	1 (2%)
Eye disorder[b]	1 (8%)	0	1 (8%)	0	0	0	0	0	0	1 (2%)
Eye inflammation[c]	0	1 (9%)	1 (8%)	2 (10%)	4	0	0	2 (7%)	4	3 (7%)
Eye irritation	1 (8%)	1 (9%)	2 (17%)	1 (5%)	1	0	0	1 (3%)	1	3 (7%)
Eye pain	1 (8%)	1 (9%)	2 (17%)	1 (5%)	1	1 (11%)	1	2 (7%)	2	4 (10%)
Eye pruritus	0	0	0	1 (5%)	2	1 (11%)	2	2 (7%)	4	2 (5%)
Eye swelling	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)
Eyelid ptosis	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)
Foreign body sensation in eyes	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)
Iritis	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)
Macular degeneration[d]	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)
Macular hole	1 (8%)	0	1 (8%)	1 (5%)	1	1 (11%)	1	2 (7%)	2	3 (7%)
Maculopathy[e]	0	1 (9%)	1 (8%)	1 (5%)	2	0	0	1 (3%)	2	2 (5%)
Ocular discomfort	0	0	0	0	0	1 (11%)	1	1(3%)	1	1 (2%)
Optic atrophy	0	1 (9%)	1 (8%)	0	0	0	0	0	0	1 (2%)
Photophobia	0	1 (9%)	1 (8%)	0	0	0	0	0	0	1 (2%)
Pseudopapilloedema	0	0	0	1 (5%)	2	0	0	1 (3%)	2	1 (2%)
Retinal deposit[f]	0	0	0	0	0	3 (33%)	3	3 (10%)	3	3 (7%)
Retinal disorder[g]	0	0	0	0	0	1 (11%)	2	1 (3%)	2	1 (2%)
Retinal haemorrhage	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)
Retinal tear	1 (8%)	0	1 (8%)	2 (10%)	2	1 (11%)	1	3 (10%)	3	4 (10%)
Infections and Infestations	**0**	**0**	**0**	**1 (5%)**	**1**	**0**	**0**	**1 (3%)**	**1**	**1 (2%)**
Conjunctivitis viral	0	0	0	1 (5%)	1	0	0	1 (3%)	1	1 (2%)
Injury, Poisoning and Procedural Complications	**0**	**0**	**0**	**0**	**0**	**1 (11%)**	**1**	**1 (3%)**	**1**	**1 (2%)**
Wound dehiscence	0	0	0	0	0	1 (11%)	1	1 (3%)	1	1 (2%)
Investigations	**1 (8%)**	**2 (18%)**	**3 (25%)**	**4 (20%)**	**5**	**1 (11%)**	**2**	**5 (17%)**	**7**	**8 (20%)**
Intraocular pressure increased	1 (8%)	2 (18%)	3 (25%)	4 (20%)	5	1 (11%)	2	5 (17%)	7	8 (20%)

[a] Cataract (CH-06) that started in Study 101, and resolved during Study 102, was reported in Study 101 only. Cataracts for CH-12 (both eyes) were reported in Study 102.
[b] Verbatim term: foveal dehiscence
[c] Including one case of endophthalmitis (verbatim term: intraocular inflammation endophthalmitis)
[d] Verbatim term: macular thinning; follow-on event to a full-thickness macular hole (resolution without surgical intervention)
[e] Includes verbatim terms of epiretinal membranes and macular pucker.
[f] Related to the vector; verbatim term: subretinal precipitate
[g] Verbatim terms: foveal thinning and loss of foveal function

The most common ocular AEs in the clinical program were conjunctival hyperaemia (22%), cataract (22%), and intraocular pressure increased (20%). The majority of ocular events were related to the administration procedure; three events of retinal deposits were related to the vector and resolved with minimal or no intervention and without sequelae.

Cataract

As of the data cut-off, there have been a total of 16 events of cataract reported in nine of 41 (22%) subjects in the clinical program. Overall, 20% of the 81 injected eyes developed cataract progression or formation.

Retinal tears

4/81 (5%) eyes in the clinical program had a retinal tear. Retinal tears were observed and repaired by the surgeon with laserpexy (fixation procedure) during the vector administration procedures in one Phase 1 subject and three Phase 3 subjects. Three events were mild in intensity, one was moderate, and all resolved with no sequelae.

Macular holes

3 subjects developed macular holes in the days after surgery, one is on-going and two are resolved.

Foveal dehiscence

One subject experienced foveal dehiscence during the surgical procedure and that resolved without intervention by Day 14.

Eyelid ptosis

1 subject was reported with mild ptosis of the left eye beginning 1121 days after the day of the first eye injection. The event was considered to be unrelated to the vector and related to the administration procedure and was ongoing (no change) at the time of the data cut-off.

Optical coherence tomography

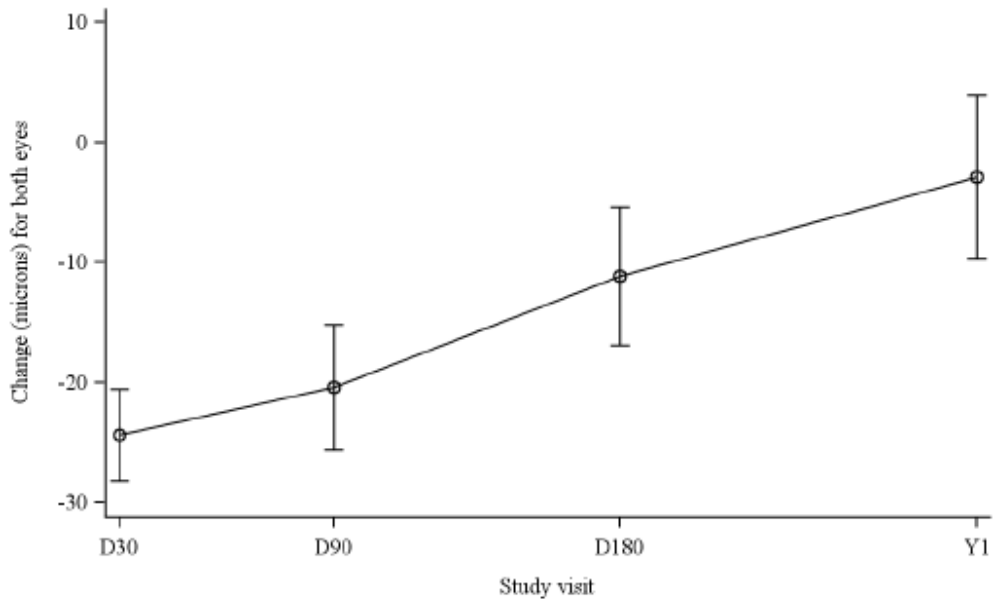
Optical coherence tomography images were captured using two different machines over the clinical program: initially using the Stratus machine and eventually using the more sensitive Heidelberg apparatus.

Optical coherence tomography is challenging due to the common presence of nystagmus. Although recent spectral domain OCT apparatus have built in eye tracking, the amplitude and frequency of nystagmus is often beyond the capability of the apparatus to maintain capture. This may detrimentally affect the resolution quality of the images captured.

In Study 101, OCT images were captured using the Stratus apparatus. For Study 102, both types of OCT instruments were used, presenting additional limitations for longitudinal review of OCT images from the Study 102 population. There was no specific pattern observed in the OCT findings.

In the Phase 3 studies, spectral domain OCT images were captured using the Heidelberg apparatus. Both eyes of the Intervention subjects had a decrease in mean foveal thickness after administration; while an increase was observed in subsequent visits, mean foveal thickness levels did not return to Baseline for either eye of the Intervention subjects. Control group changes were minimal for both eyes.

Figure 14 Heidelberg Retina Tomography: Change in Foveal Thickness (Microns) for Both Eyes (301+302, n=29)



Data presented as mean ± SE.
Data source: Module 5.3.5.3, Study 301, Figure 14.3.4.1

The decrease in foveal thickness could be attributed to decreased length of the outer segments following bleb formation and retinal detachment, with delayed elongation after re-attachment.

While a statistically significant difference was observed, it is not clear whether the mean decrease of 13.1 microns in the first injected eye of the Intervention group subjects is clinically relevant and / or greater than the expected variability for this anatomical assessment, particularly in individuals with RPE65 mutations and considering variations in precise anatomical locations from visit to visit; the range of change observed for this outcome at Year 1 was -87 to 183 microns for the Intervention group and -13 to 15 for the Control group.

Time domain OCT images were captured using the Stratus apparatus (Children's Hospital of Philadelphia [CHOP] site only). No significant difference between the Intervention or Control subjects was observed by Stratus measures of foveal thickness at Year 1. The minimal changes observed for both groups may be due to the variability in fixation.

Overall, it was not clear whether the observed decreases were clinically relevant and/or greater than the expected test-retest variability for individuals with RPE65 mutations, particularly when taking variations in precise anatomical locations from visit to visit into consideration; however, in looking across data for all subjects from injection baseline to Year 1 post administration, one can appreciate that, on average, the reduction in foveal thickness observed at Day 30 post administration using Heidelberg OCT (range: -20.1 to -34.3 microns) appeared to be temporary, with a return to injection Baseline levels observed by Year 1. These findings may represent a reversible disruption of the outer segments of the retina observed during the postoperative period.

Serious adverse event / deaths / other significant events

Deaths

No deaths were reported during the clinical development program up to the cut-off date.

Serious Adverse Events

Through the 05-May-2017 data cut-off, 14 SAEs have been reported in nine subjects in the clinical program (Table 16):

Table 15 Serious Adverse Events by SOC and PT – All Studies, Data Cut-Off 05-May-2017

Number (%) of Subjects MedDRA SOC / PT	Phase 1			Phase 3				Total Phase 1 + Phase 3 (N = 41)
				Study 301		Study 302		
	Study 101 (N = 12)	Study 102 (N = 11)	Total (N = 12)	Inter-vention (N = 20)	Control (N = 9)	Control/ Inter-vention (N = 9)	Total 301 / 302 (N = 29)	
Subjects with at least 1 SAE	**1 (8%)**	**3 (27%)**	**4 (33%)**	**2 (10%)**	**0**	**1 (11%)**	**3 (10%)**	**7 (17%)**
Gastrointestinal disorders/ Anal fistula	1	0	1	0	0	0	0	1 (2%)
Injury, Poisoning & Procedural Complications / Lower limb fracture		1						1 (2%)
Investigations/ Intraocular pressure increased	0	1[a]	1	0	0	0	0	1 (2%)
Congenital, familial and genetic disorders/ Cryptorchism	0	1	1	0	0	0	0	1 (2%)
Nervous system disorder/ Paraesthesia	0	1	1	0	0	0	0	1 (2%)
Nervous system disorders/ Convulsion	0	0	0	1	0	0	1	1 (2%)
General disorders and administration site conditions/ Adverse drug reaction	0	0	0	2	0	0	2	2 (5%)
Reproductive system and breast disorders/ Menorrhagia[F]				1				1 (4%)
Infections and infestations/ Pneumonia				1				1 (2%)
Eye disorders/ Retinal disorder	0	0	0	0	0	1	1	1 (2%)

Shaded cells - Related to participation in the study (complications resulting from the administration procedure).
[F] Denominator includes only subjects who are female in each study.
[a] Secondary to treatment for a resolved endophthalmitis event related to the administration procedure
Source data: Module 5.3.5.3, 120-Day Safety Update, Study 101, Listing 16.2.7.3; Module 5.3.5.3, 120-Day Safety Update, Study 102, Listing 16.2.7.3; Module 5.3.5.3, 120-Day Safety Update, Study 301, Listing 16.2.7.4 and Listing 16.2.7.1.1.1.

Most serious adverse events were unrelated to participation in the clinical studies and none were related to AAV2-hRPE65v2; one serious TEAE (intraocular pressure increased) was reported as a result of treatment for endophthalmitis that led to elevated intraocular pressure, with subsequent optic atrophy, and one serious TEAE (retinal disorder [loss of foveal function]) was assessed as probably related to the administration procedure.

Immunological events

Cell-mediated and humoral immune responses

Data have not shown any specific pattern or clinical correlates. There was substantial subject-to-subject variability in anti-AAV2 titre both prior to and following vector administration. The clinical significance of the changes in anti- AAV2 titre following vector administration is unknown.

No clinical inflammatory response to the investigational product has been observed and no dose limiting toxicity was seen in the clinical program.

Vector Shedding Data

For the Original Intervention subjects:

- all samples tested were negative in 11 subjects
- 8 subjects had only positive tear samples
- 1 subject had only positive serum samples
- 1 subject had both positive tear and serum samples
- In 6 subjects, there was only one positive sample from tears at Day 1 post injection
- 2 subjects tested positive for tears up to day 10 after the first eye administration.
- In both subjects with detectable vector in serum, levels were low (from 13 to 68 copies) and only detectable up to Day 3 following each injection.

In Control / Intervention subjects:

- all samples tested were negative in 4 subjects
- 4 subjects had only positive tear samples
- 1 subject had both positive tear and serum samples.
- Positive tear / serum samples were found up to Day 14.
- In the one Control / Intervention subject with detectable vector in serum, the levels were low (ranging from 21 to 24 copies) and only detectable up to Day 3B.

Laboratory findings

Routine laboratory safety

No pattern of change detected.

Cell-mediated and humoral immune responses

Data collection for the analysis of cell-mediated and humoral immune responses ceased prior to the time period of this addendum. More specifically, for Study 102 subjects, cell-mediated and humoral immune responses were no longer assessed following transfer to the LTFU protocol while for Study 301, these responses were not assessed after Year 1B.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

41 subjects aged 4 to 45 years, male and female, received AAV2-hRPE65v2 (bilateral injection, n = 40 [98%]; unilateral injection, n = 1 [2%]). All subjects had a confirmed molecular diagnosis of an RPE65 gene mutation. The small number of subjects and consequent limited experience of exposure to study drug is understood in the context of a rare disease.

The safety data were collected up to the revised cut-off date (5-May-2017),

The safety data evaluated correspond to an initial 1 year of observation and to a long-term phase of observation (up to 4-7 years for phase 1 subjects and up to 2-3 years for phase 3 subjects). Although the period of long term follow-up is acceptable, more data with longer periods could raise new safety information or add information that better clarifies the uncertainties about the clinical significance of some the safety findings.

It should be mentioned that there is a significant heterogeneity of the target population due to different subtypes of the mutation and different clinical diseases associated to the mutation, that could have impact on the evolution and clinical features of the disease that could influence the benefit/risk profile of the treatment. With the current data, it seems that there is no association between mutation type and baseline disease state, treatment response and apparent risk of ocular events and that the overall benefit/risk profile of voretigene neparvovec cannot be predicted a priori by assessment of mutation subtype.

Overall, available safety data from the voretigene neparvovec clinical program demonstrate that the intervention was generally well tolerated.

All subjects (100%) reported at least one AE while on study. Most adverse events were mild and most resolved without sequalae, but there were eight serious AEs in seven subjects and also a few AEs or SAEs that resolved with sequalae.

The most frequent AEs by SOC for all 29 Phase 3 subjects during the first year post injection were Gastrointestinal Disorders (n = 17 subjects, 59%), Eye Disorders (n = 16 subjects, 55%), and Nervous System Disorders (n = 16 subjects, 55%). At the PT level, the most frequent events were headache (n = 13 subjects, 45%), leukocytosis (n = 11 subjects, 38%), nausea (n = 10 subjects, 35%), and vomiting (n = 10 subjects, 35%). Most of them, except of Eye Disorders were not related to the vector or to the administration procedure.

69% of subjects reported TEAEs considered related to the administration procedure and of special concern are that two of them were SAEs (permanent loss of foveal function and intraocular pressure increase Grade 4) with clinical relevance.

Most of the ocular TEAEs were known complications of intraocular surgery and occurred during the initial year of post-administration follow-up; these were: increased intraocular pressure, retinal tear, macular hole, cataract, and inflammation and / or infection of the eye post-administration.

The only TEAEs that were considered related to AAV2-hRPE65v2 were 3 TEAEs of retinal deposit (probably related to AAV2-hRPE65v2 but not to the administration procedure); they were reported in three subjects and were transient, asymptomatic fundoscopic findings with no observed clinical correlate; all resolved by 8 weeks.

Another aspect that should be considered is the expertise and training of the sites and personnel participating in the clinical program that could not be extrapolated to other sites and personnel. In the Risk Management Plan of the product, some minimisation measures have been proposed for the risks related with the administration procedure including the distribution through centres of excellence who have received adequate training on use of product and an educational programme with multiple measures. This seems reasonable, but the implementation of the proposal could be complex due to Health Management Systems quite different from country to country although the minimum level of adequate specific training and standardization seems that could be reached with the proposed educational programme.

Although the changes in the cell-mediated and humoral immune responses seem to be minimal, the clinical significance is not clear and this creates an uncertainty for the safety assessment of voretigene neparvovec.

The uncertainties about immune responses could have higher weight if in the future repeat administration of voretigene neparvovec is necessary to treat an individual eye, as currently there are no available data for this repeated administration.

Longer follow-up and a higher number of patients exposed to voretigene neparvovec will help to better outline the safety profile of the new treatment and its real benefit for the target population. The ongoing follow-up for patients included in the clinical program and the registry planned to collect long term safety data in patients treated with voretigene neparvovec included as pharmacovigilance activities in the Risk Management Plan was deemed to be appropriate.

2.6.2. Conclusions on the clinical safety

The limited experience of exposure to study drug is understood in the context of a rare disease. The company intends to follow-up subjects exposed to study drug for 15 years.

The CHMP endorses the CAT conclusion on clinical safety as described above.

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns

Important identified risks	Increased intraocular pressure Retinal tear Macular disorders Cataract Intraocular inflammation and/or infection related to the procedure Retinal detachment
Important potential risks	Tumorigenicity Host immune response Third party transmission
Missing information	Long term efficacy (> 4 years) Use in pregnancy and lactation Use in children < 3 years of age Long-term safety (> 9 years)

Pharmacovigilance plan

Ongoing and planned studies in the Pharmacovigilance Plan

Activity / Study title	Objectives	Safety concerns addressed	Milestones	Due dates
SPKRPE-EUPASS A Post-Authorization, Multicenter, Multinational, Longitudinal, Observational Safety Registry for Patients Treated with Voretigene Neparvovec in Europe Planned ***Category 1***	This is a single-group, prospective, observational, multicenter (i.e. in Ocular Gene Therapy Treatment Centres and inherited retinal dystrophy referral sites) registry designed to collect data on long term safety outcomes in patients treated with voretigene neparvovec.	Increased IOP Retinal tear Macular disorders Cataract Intraocular inflammation and/or infection related to the procedure Retinal detachment Tumorigenicity Host immune response Third party transmission Lack of efficacy and/or decline in efficacy over time Use in pregnancy and lactation Use in patients < 3 years of age	Study starting Progress reports Final report	31 December 2019 Annually 30 June 2030
LTFU-01 A Long-Term Follow-Up Study in Subjects Who Received an Adenovirus-Associated Viral Vector Serotype 2 Containing the Human RPE65 Gene (AAV2-hRPE65v2) Administered via Subretinal Injection Ongoing ***Category 1***	Study AAV2-hRPE65v2-LTFU-01 is a long-term safety and efficacy follow-up study of trial participants who received voretigene neparvovec in the clinical programme	Increased IOP Retinal tear Macular disorders Cataract Intraocular inflammation and/or infection related to the procedure Retinal detachment Tumorigenicity Host immune response Use in pregnancy and lactation Long-term efficacy (> 4 years) Long-term safety (> 9 years)	LTFU annual progress reports 15- year follow-up (Last patient last visit) Study finish and final report	Annually 31 December 2030 31 December 2031

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligationsCategory 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Increased intraocular pressure	SmPC sections 4.4 and 4.8 PL sections 2 and 4 Recommendation for patients to avoid air travel or other travel to high elevations until the air bubble formed as a result of Luxturna administration has dissipated from the eye, which should be verified by an ophthalmic examination in SmPC section 4.4 and PL section 2 Prescription only product Distribution through treatment centres who have received mandatory training on use of product Patient card	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe Long-term follow-up study for participants in the clinical programme
Retinal tear	SmPC sections 4.4 and 4.8 PL sections 2 and 4 PL section 2 contains advice for patients regarding which symptoms they should contact the doctor for Prescription only product Distribution through treatment centres who have received mandatory training on use of product Patient card	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe Long-term follow-up study for participants in the clinical programme
Macular disorders	SmPC sections 4.4 and 4.8 PL sections 2 and 4 Advice in SmPC section 4.4 on where Luxturna should not be administered PL section 2 contains advice for patients regarding which symptoms they should contact the doctor for Prescription only product Distribution through treatment centres who have received mandatory training on use of product Patient card	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec Long-term follow-up study for participants in the clinical programme
Cataract	SmPC section 4.8 PL sections 2 and 4 PL section 2 contains advice for patients	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	regarding which symptoms they should contact the doctor for Prescription only product Distribution through treatment centres who have received mandatory training on use of product Patient card	Long-term follow-up study for participants in the clinical programme
Intraocular inflammation and/or infection related to the procedure	SmPC sections 4.2, 4.3, 4.4 and 4.8 PL sections 2 and 4 Guidance regarding aseptic technique and use of topical microbicide in SmPC section 4.2. States what symptoms the patients need to be informed to report without delay in section 4.4 PL section 2 contains advice for patients regarding which symptoms they should contact the doctor for Avoidance of swimming in SmPC section 4.4 and PL section 2. Prescription only product Distribution through treatment centres who have received mandatory training on use of product Patient card	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe Long-term follow-up study for participants in the clinical programme
Retinal detachment	SmPC sections 4.2 and 4.4. PL sections 2 and 4 States what symptoms the patients need to be informed to report without delay in section 4.4 PL section 2 contains advice for patients regarding which symptoms they should contact the doctor for Prescription only product Distribution through treatment centres who have received mandatory training on use of product Patient card	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe Long-term follow-up study forparticipants in the clinical programme
Tumorigenicity	Prescription only product	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe Long-term follow-up study for participants in the clinical programme

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Host immune response	SmPC section 4.2. PL section 3. The immunomodulatory regime to be used is stated in the SmPC section 4.2 and referenced PL section 3 Prescription only product	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe Long-term follow-up study for participants in the clinical programme
Third party transmission	SmPC sections 4.4, 5.2 and 6.6. Advice on how to handle waste material from dressings, tears and nasal secretions and on personal protective equipment in section 4.4. An exclusion from donation of blood, organs, tissues, and cells for transplantation is included. Advice on managing accidental exposure is in section 6.6 PL section 2 provides advice on personal protective equipment and disposal of dressings and waste materials. An exclusion from donation of blood, organs, tissues, and cells for transplantation is included. Prescription only product Patient card	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe
Long-term efficacy (> 4 years)	Prescription only product	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe Long-term follow-up study for participants in the clinical programme
Use in pregnancy and lactation	SmPC section 4.6 PL section 2 Prescription only product	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec Long-term follow-up study for participants in the clinical programme
Use in children < 3 years of age	SmPC section 4.2 PL section 2 Prescription only product	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety (> 9 years)	Prescription only product	Long-term follow-up study for participants in the clinical programme

Conclusion

The CHMP, CAT and PRAC considered that the RMP version 1.4 (dated 18 September 2018) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP and CAT considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The IBD is 19/12/2017. The applicant did request international harmonisation of the PSUR cycle by using the forthcoming Data Lock Point 24/07/2007 (data harmonised with DIBD).

2.9. New Active Substance

The applicant declared that voretigene neparvovec has not been previously authorised in a medicinal product in the European Union.

The CHMP and CAT, based on the available data, consider voretigene neparvovec to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The company has requested an exemption from printing the statement '*Keep out of the sight and reach of children*' on the pouch label and on the outer carton, based on Art. 63(3) which was accepted

by the QRD Group. The proposed omission of the warning for children will have no adverse impact on the correct administration safety of the product based on the fact that the product will be supplied to a limited number of specialised clinical centres and excluded handled by healthcare professionals.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

A request for an exemption of the labelling as per Art.63.3 of Directive 2001/83/EC in relation to severe problems in respect of the availability of the medicinal product has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The company has submitted a request to use the US vial label (for the concentrate and solvent) in Europe because of manufacturing issues. This will be a temporary measure until Q1 2020.

Luxturna was approved in the US in December 2017. Only a few thousand people worldwide are affected, and there are no other existing therapies for this rare blinding condition. In Europe, orphan medicinal designation for Leber congenital amaurosis was granted in April 2012 (EU/3/12/981) and for treatment of retinitis pigmentosa in July 2015 (EU/3/15/1518).

For approximately the first year following the anticipated EC approval of voretigene neparvovec in the fourth quarter of 2018, drug supply for Europe will be severely limited due to long manufacturing lead times.

Given the rarity of the disease, the manufacturing batch size is small, due to the small number of patients and the dose given. Only a very limited amount of the US drug product is available until early 2020, when the first batches intended for the European market are manufactured. The applicant anticipates providing access to approximately 80-90 patients by the end of 2019. This request to use the US labelled vial is therefore temporary in nature, and will be extremely limited in scope. Alternative labelling of the frozen vial (i.e. frozen vials are thawed to ambient temperature, re-labelled, and then refrozen.) is not possible. This would require the Applicant to qualify this thawing process prior to implementation. Exceptionally, use of the currently available vials as labelled for the US market, is the most direct pathway to supply Europe for a short temporary timeframe until Q1 2020.

Because of the complexity of this request, this was assessed by the QRD Group.

Based on the above arguments, the QRD members agreed to have the vial marketed with the US label with the following comments:

- Distribution of the US pack in the EU should be accompanied by a communication letter informing HCPs about the US vials and its differences compared to the EU vial label, as follow:

    - Clarification on what does the sentence ‘Rx only’ means and why it appears on the label (only applicable to US market)

    - To re-emphasise in particular the need for dilution before use as the Ph. Form ‘concentrate’ is not mentioned on the US pack and the dilution step is not prominent enough.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Luxturna (voretigene neparvovec) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU. In addition, it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Leber's congenital amaurosis type 2 and retinitis pigmentosa Type 20 are diseases of the eye inherited in an autosomal recessive manner. Subjects may progressively lose visual acuity and visual fields from birth; the rate of loss accelerates from the late teenage years. Night blindness is a feature of the condition.

Symptoms may become evident from 2 – 3 months of age. There is progressive, profound reduction of visual acuity, concentric reduction of visual fields, night blindness and nystagmus. Subjects have great difficulty performing activities of daily living, even under normal daytime lighting conditions. Subjects may be blind by young adulthood. Subjects with this condition have a deficiency of activity of all-trans-retinyl isomerase, one of the enzymes involved in the biochemistry of light capture by the cells of the retina. All-trans-retinyl isomerase is encoded by the RPE65 gene. Subjects have mutations in the RPE65 gene.

Luxturna is a gene therapy that delivers hRPE65 to the cells of the retina. Once installed in to a patient, expression of the gene product of hRPE65, all-trans-retinyl isomerase, will permit subjects to regenerate intra-ocular 11-cis-retinal and so lead to improvement in the ability to detect light.

In the course of the MAA evaluation it became apparent that for a gene therapy product like luxturna, an indication based on a molecular/genetic diagnosis would be more appropriate than an indication based on clinical classification/description. Consequently, the indication was revised to "inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations " as this allows for more precise definition of the underlying biology of the disease and embraces different clinical descriptions including LCA and retinitis pigmentosa, while clearly indicating only the specific mutation that is amenable to therapy with Luxturna. This approach was endorsed by the convened Expert Group meeting (see section 2.5.3).

3.1.2. Available therapies and unmet medical need

There is not a licenced medicinal product for inherited retinal dystrophy owing to biallelic RPE 65 mutations / medical management is supportive.

Surgical devices are available for subjects who meet clinical requirements: either the Argus® II Retinal Prosthesis System or the Alpha AMS Retina Implant AG. The devices have variable and limited clinical efficacy. There is an unmet clinical need.

3.1.3. Main clinical studies

The company conducted exploratory clinical studies 101 and 102 in 11 subjects with Leber's congential amaurosis type 2 in order to gain experience with product and in order to develop its in-house mobility tool (a test of vision function). These studies were open label, uncontrolled and non-randomised.

The main clinical study was study 301/302. This study was open-label, randomised and controlled. 29 subjects with Leber's congential amaurosis type 2 were recruited; 20 subjects were exposed to study drug whilst 9 subjects entered a control arm and were followed for one year before being exposed to study drug i.e. delayed entry design.

Viable retinal cells need to be present for Luxturna to exert an effect. Thus, participants in the Phase III study had to be shown to have sufficient viable retinal cells defined for the purpose of the study as an area of retina within the posterior pole of >100 µm thickness as determined by optical coherence tomography. In the opinion of the principal investigators (retinal surgeons) for the company, this was the minimum retinal thickness required in order to safely perform the administration procedure; retinal thickness was chosen as the best available surrogate for retinal viability in the absence of a suitable test to directly measure viability.

Outcome as assessed by a mobility test tool (developed in-house by the company) has been used as the primary endpoint of study 301/302. The mobility test tool is a clinic-based clinician-reported outcome assessment tool. Subjects are asked to navigate between start and finish in a stylised obstacle course at ambient light set at one constant level between 400 lux and 1 lux during each attempt. The main analysis was of binocular navigation of the test layout.

Subjects are marked as either 'pass' or 'fail'; a 'pass' mark requires the subject to complete the task within 180 secs and to 'fail to navigate' 3 or less obstacles. A 'pass' mark at 1 lux is the highest possible score.

At baseline, subjects scored pass marks in the mobility test at between 4 and 400 ambient lux i.e. there was much variation in competence at baseline.

3.2. Favourable effects

The evaluation of efficacy mainly relies on the effect on vision under low light conditions, as nyctalopia (an abnormal inability to see in dim light) represents one of the key clinical features of the disease. After 1 year the patients treated with voretigene neparvovec improved, with respect to baseline performance and to controls, and were able to better navigate an indoor stylised course at lower ambient light level. This was reflected in their results on the used navigation tool score. Control un-injected patients did not change their mean score. A difference of 1.6 score between groups was observed. This MT change score difference was statistically significant (p= 0.001). For the ITT population, 13 of 21 (62%) subjects in the Intervention group passed at 1 lux (maximum score of 6) at Year 1 versus 0/10 in the Control group. This magnitude of change was also observed when each

eye was considered separately.

The effect has been maintained for up to 3 years.

The meaningful aspect of health that is addressed by the mobility test is “ambulatory vision” or how the individual uses vision to navigate around obstacles and from place to place. Thus, in patients with RPE65 mutation-associated retinal dystrophy, nyctalopia is a hallmark of the disease and vision, particularly in dim light, is profoundly impaired and so limits, or prevents, the ability to perform multiple activities that are part of normal life, particularly those that take place in low illuminance environments. This impairment is meaningful to the patient, something the patient cares about, and in the context of a progressive, degenerative disease, a treatment that improves or prevents worsening is viewed as beneficial.

Secondary endpoints of full field sensitivity of the retina, monocular navigation of the mobility test layout and change in visual acuity are generally supportive towards the primary endpoint as measured by the mobility test tool of the company. Outcomes of the primary endpoint for subjects also appear to be confirmed by post-test interviews conducted with subjects regarding ability to function in a home setting.

3.3. Uncertainties and limitations about favourable effects

Although it is considered that the mobility test tool has notable deficiencies such as a broad ceiling effect that will hamper follow-up, the tool is considered to be a reasonable attempt to record visual function under a variety of conditions. Nonetheless, simply watching videos of subjects undergoing the mobility test before and after exposure to Luxturna convinces of clinical efficacy without recourse to review scores of the mobility test. It is noted that the company has decided not to develop the mobility tool further.

There are technical difficulties in carrying out retinal surgery in subjects under the age of 3yrs and so the company did not include subjects younger than 3 years in the clinical studies.

Neither age of the subject nor genotype were able to identify subjects who would or would not respond to exposure to Luxturna, presumably as a result of the heterogeneity of presentation and progress of the disease.

Long-term efficacy beyond 3 years after exposure to Luxturna has not yet been established and so measurements of efficacy should be recorded beyond 3 years after exposure to the current product in order to substantiate long-term maintenance of clinical effect.

In addition, questions related to the need for additional re-treatments in cases of loss of effect or the administration of multiple injections in order to widen the target retinal area would be of interest to address.

3.4. Unfavourable effects

Luxturna is delivered to the sub-retinal space of the eye by a surgical procedure. Unfavourable effects were mostly confined to the eye.

Three subjects showed evidence of retinal deposit after exposure to Luxturna. These deposits were considered related to study drug and were transient, asymptomatic fundoscopic findings with no observed clinical correlate; all resolved by 8 weeks.

Most of the ocular treatment-emergent adverse events were known complications of intraocular surgery and occurred during the initial year of post-administration follow-up; these were: increased

intraocular pressure, retinal tear, macular hole, cataract, foveal dehiscence, retinal hemorrhage and inflammation and / or infection of the eye post-administration. These events might have long-term consequences, especially if they were left untreated. The company has submitted published data that are comparable to the complications of pars plana eye surgery reported for the current studies.

Through the data cut-off, eight serious TEAEs in seven subjects have been reported in the clinical program. Most were unrelated to participation in the clinical studies and none were related to AAV2-hRPE65v2; one subject experienced a SAE (significant and permanent loss of foveal function) related to the administration procedure, and one subject reported a SAE (intraocular pressure increased grade 4) related to treatment (periocular steroid) for an AE (endophthalmitis) that was related to the administration procedure. These two SAEs took place in subjects older than 18.

In Phase III, there were changes in the foveal thickness for same patients after drug administration that in some cases returned to baseline levels after 1 Year and not in others.

In Phase III, the three TEAEs of retinal deposit and the three TEAEs of retinal tear all occurred in subjects under the age of 18 (15% vs. 0%). The incidence of TEAEs related to the administration procedure in Phase 3 was double for subjects aged $\geqslant$ 18 years (100%) compared to subjects aged < 18 years (50%). This difference was especially evident in the Eye Disorders, which showed a higher incidence of AEs related to the administration procedure in older subjects (78%) than in younger subjects (30%). No marked differences were observed for TEAEs by severity.

There were isolated changes in the cell-mediated and humoral immune responses and also some cases of positive results (low levels and transient) for vector shedding in tears and/or serum.

Update July 2018: the company reports on 4 instances of retinal tear and one serious adverse event of retinal detachment.

3.5. Uncertainties and limitations about unfavourable effects

The small population of only 41 subjects exposed in total with follow-up for most being only up to 3 years inevitably means that knowledge of unfavourable effects is much limited. This may be addressed by each subject entering into a 15-year follow-up programme, as proposed by the company.

The open-label nature of study 301/302 inevitably means that the true magnitude of benefit may be smaller than that claimed by the company.

There was heterogeneity of the target population (perhaps owing to subjects having different mutations of the RPE65 gene) reflected in variation of clinical features of the disease and that may affect the benefit / risk profile of the treatment in each recipient.

Adverse events not so far reported may become apparent as more subjects are exposed to the current product. Similarly, the frequency of adverse events now reported may be revised as there is more experience of use of the current product.

It is not known if the expertise and training of personnel at the sites in the clinical programme will be matched by sites recruited in the post-licensing phase.

Information on exposure to children under 3 years old is missing.

Although the changes in the cell-mediated and humoral immune responses seem to be minimal and the levels of vector shedding seem to be low and transient (positive findings mainly in tears), the clinical significance is not clear.

The uncertainties about immune responses could have higher weight if in the future repeat administration of voretigene neparvovec is necessary to treat an individual eye, as currently there are no available data for this repeated administration.

3.6. Effects Table

Table 16 Effects Table for Luxturna in the indication of Leber's congenital amaurosis type 2 (data cut-off for study 301/2: 16 July 2015)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Multi-luminance mobility test (MLMT) Change in MLMT score 1 year after exposure and using binocular vision	The mobility test tool is a clinic-based clinician-reported outcome assessment tool. Subjects are asked to navigate between start and finish in a stylised obstacle course at ambient light set at one level between 400 lux and 1 lux during each attempt. The main analysis was of binocular navigation of the test layout. Top mark is 'pass' at 1 lux.	Subjects are marked as either 'pass' or 'fail'; a 'pass' mark requires the subject to complete the task within 180 secs and to 'fail to navigate' 3 or less obstacles. A 'pass' mark at 1 lux is the highest possible score. Marks from -1 (fail at 400 lux), 0 (pass at 400 lux) to 6 (pass at 1 lux, best pass mark) i.e. ordinal units	Difference (95% CI) Intervention-Control = 1.6 (0.72, 2.41), p-value <0.001	A change of ±1 unit noted during control phase	The multi-luminance mobility test has a notable ceiling effect that may hinder follow-up to detect loss of efficacy [if this occurs]. Current data suggest that improved visual ability persists for 3 years.	[1]

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Full field sensitivity test	Average light sensitivity of the entire visual field for white light at Year 1 after exposure as compared to Baseline light sensitivity testing.	Log10 [candela second per metre squared]	First assigned eye (ITT): Difference (95% CI) (Intervention-Control) = -2.33 (-3.44, -1.22), p<0.001 Second assigned eye (ITT): Difference (95% CI) (Intervention-Control) = -1.89 (-3.03, -0.75), p<0.002	No change	Improvement in full field sensitivity was maintained for up to 3 years of follow-up full field sensitivity data support the	[1]

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Visual acuity	ETDRS or HOTV charts used or description-type assessment for grossly impaired acuity and conversion to LogMAR units	LogMAR units	At one year after exposure to voretigene neparvovec, improvement in visual acuity of at least 0.3 LogMAR occurred in 11 (55%) of the first-treated eyes and 4 (20%) of the second-treated eyes	no one in the control group displayed an improvement of visual acuity in either the first or second eye.	primary endpoint Visual acuity data are generally supportive towards the primary endpoint	
Unfavourable Effects						
Adverse events Related to Luxturna	Retinal pigment deposition		Found in 3 subjects		Transient / no clinical consequence	[1]
Adverse events related to eye surgery	Physical disruption of the tissues of the eye		All subjects		similar in nature and prevalence to published data on eye surgery	[1]

Abbreviations: LogMAR, logarithm of minimal angle of resolution. ETDRS, Early Treatment Diabetic Retinopathy Study.Notes: [1] = study 301/302

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Increased sensitivity of the retina to light is highly relevant and highly important to subjects with inherited retinal dystrophy, a condition where an unmet clinical need exists. The consequence of improved functional vision may be expected to much enhance quality of life for these subjects.

Transient retinal pigment formation without clinical consequence and that resolves within 8 weeks is considered to be an unfavourable effect, which is outbalanced by the positive effects of the treatment.

The complications of pars plana eye surgery reported by the company are recognised complications of such surgery and are inevitable. These are important unfavourable effects. Though not to be taken lightly, it is usual practice for risks of surgery to be explained to the subject prior to surgery so that the subject may develop his / her own risk assessment. The complications of surgery also reflect the competence of the surgeon; it is intended that such surgery is done by a skilled surgeon. In these contexts, the unfavourable effects of surgery are considered to be manageable.

More data with longer periods could raise new safety information or add information that better clarifies the uncertainties about the clinical significance of some the safety findings. An update of safety data may be of relevance to better characterise the safety profile of voretigene neparvovec.

3.7.2. Balance of benefits and risks

The clinical benefit of improved detection of light far outweighs the complications of eye surgery.

The benefit/risk balance is currently positive for subjects with a diagnosis of inherited retinal dystrophy owing to biallelic RPE 65 mutations.

3.7.3. Additional considerations on the benefit-risk balance

It is acknowledged that the number of patients with biallelic RPE 65 mutations treated with Luxturna is small, and it may not fully cover the range of phenotypic expression (and probably the nomenclature of diagnosed conditions) in terms of severity of the visual function loss that may be observed in clinical practice. Nevertheless, this is a gene therapy product which is designed to restore a specific loss of function caused by single gene (RPE 65) mutation. The clinical data reflects that the essential pre-requisite for the product to work is the existence of 'sufficient viable retinal cells'. The study included patients with significant visual function loss (visual acuity ≤20/60 and/or visual field ≤ 20 degrees for both eyes) and provided adequate evidence of efficacy in this group. It is further acknowledged that based on the understanding of the mechanism, it is highly likely to benefit patients with lesser visual function loss as these patients will have more viable retinal cells. Any limitation to use in patients with better preserved visual function will be based on limitations of long-term safety data and not owing to uncertainties on efficacy. Given this understanding it was not considered appropriate to restrict the use of the gene therapy based on extent / pattern of visual loss.

Based on the above considerations, a limitation based on specific phenotypic types was not considered appropriate. However, further studies that would be recommended are:

- Long-term follow-up of recipients of Luxturna to establish continuing efficacy and safety.

3.8. Conclusions

The overall B/R of Luxturna is positive in the agreed indication.

The CHMP endorses the CAT conclusion on Benefit Risk balance as described above.

4. Recommendations

Outcome

Based on the draft CHMP opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit- risk balance of Luxturna is favourable in the following indication:
Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of LUXTURNA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each Member State (MS) where LUXTURNA is marketed, the product is distributed through treatment centres where qualified staff (i.e. vitreoretinal surgeons and pharmacists) have participated in the mandatory educational program about use of the product and pharmacy training, in order to ensure LUXTURNA correct use so as to minimise the risks associated with its administration and / or the administration procedure (increased intraocular pressure, retinal tear, macular disorders, cataract, intraocular inflammation and/or infection related to the procedure and retinal detachment, third party transmission).

Criteria for Study sites/treatment centres should include:

1. Presence of a specialist ophthalmologist with expertise in care and treatment of patients with inherited retinal dystrophy (IRD);
2. Presence of or affiliation with a retinal surgeon experienced in sub-retinal surgery and capable of administrating LUXTURNA;
3. Presence of a clinical pharmacy capable of handling and preparing AAV vector-based gene therapy products;

Training and instructions for safe handling and disposal of affected materials for 14 days following product administration should also be provided along with information regarding exclusion from donation of blood, organs, tissues, and cells for transplantation after LUXTURNA administration.

The qualified staff (i.e. vitreoretinal surgeons and pharmacists) at the treatment centres should be provided with educational materials including:

- Summary of Product Characteristics (SmPC);

- Surgical education for LUXTURNA administration, including description of materials and procedures needed to perform LUXTURNA sub-retinal injection

  Or

- Pharmacy training manual, including information on LUXTURNA preparation and storage;

Patients and their caregivers should be provided with the patient information pack, including:

- Patient Information Leaflet (PIL), which should also be available in alternative formats (including large print and as audio file);
- A patient card
    - Highlights the importance of follow-up visits and reporting side effects to the patient's physician.
    - Inform healthcare professionals that the patient has received gene therapy, and the importance of reporting adverse events.
    - Contact information for adverse event reporting.
    - Patient card will be available in alternative formats including large print and as an audio file. Information on how to obtain the special formats will be provided in the patient card.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
SPKRPE-EUPASS: Non-interventional PASS: In order to further characterize the safety including long-term safety of Luxturna, the applicant should conduct and submit a study based on data from a disease registry in patients vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations.	30 June 2030
AAV2-hRPE65v2-LTFU-01: In order to further evaluate the long-term efficacy and safety outcomes of Luxturna in adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations, the applicant should submit the long-term efficacy and safety follow-up of trial participants who received Luxturna in the clinical programme (15- year follow-up).	31 December 2031

The CHMP endorses the CAT conclusion on the obligation to conduct post-authorisation measures as described above.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CAT review of the available data, the CAT considers that voretigene neparvovec is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

The CHMP endorses the CAT conclusion on the new active substance status claim.

Paediatric Data

Furthermore, the CHMP and CAT reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0221/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.