Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Voretigene neparvovec

Proprietary Product Name: Luxturna

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

December 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AAV2	Adeno-associated virus serotype 2
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
bp	Base pair
cd.s/m^2	Candela second per metre squared
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments of 1988 (United States law)
ELISpot	Enzyme-linked immune absorbent spot
EMA	European Medicines Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States)
FST	Full-field light sensitivity threshold, or full field scotopic threshold
IFN-γ	Interferon gamma
ILAC	International Laboratory Accreditation Cooperation
IRD	Inherited retinal dystrophies
ITT	Intention to treat
LCA	Leber congenital amaurosis
LogMAR	Logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
MLMT	Multi luminance mobility testing
NATA	National Association of Testing Authorities
OGTR	Office of the Gene Technology Regulator, Australian Government Department of Health

Abbreviation	Meaning
OCT	Optical coherence tomography
PI	Product Information
RMP	Risk management plan
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelium
RPE65	Retinal pigment epithelium 65 kDA protein
RPE65	RPE65 gene
SD	Standard deviation
SE	Standard error of the mean
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
US	United States of America
VA	Visual acuity
VF	Visual field
VFQ-25	Visual Function Questionnaire 25
vg	Vector genome

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Luxturna
Active ingredient:	Voretigene neparvovec
Decision:	Approved
Date of decision:	4 August 2020
Date of entry onto ARTG:	5 August 2020
ARTG number:	318929
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road Macquarie Park NSW 2113
Dose form:	Concentrated solution for injection vial with diluent ampoule
Strength:	5 x 10^{12} vector genomes (vg) per mL
Container:	Vial
Pack size	One vial of concentrated solution for injection, two ampoules of diluent
Approved therapeutic use:	*Treatment of patients with inherited retinal dystrophy caused by pathological biallelic RPE65 mutations and who have sufficient viable retinal cells as determined by the treating physician.* *Pathological mutations of RPE65 should be confirmed by a National Association of Testing Authorities (NATA) or International Laboratory Accreditation Cooperation (ILAC) accredited laboratory.*
Route of administration:	Subretinal injection

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Dosage:	Treatment should be initiated and administered by a retinal surgeon experienced in performing macular surgery. Patients will receive a single dose of 1.5×10^{11} vg of Luxturna in each eye. Each dose will be delivered into the subretinal space in a total volume of 0.3 mL. The individual administration procedure to each eye is performed on separate days within a close interval, but no fewer than 6 days apart. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	B2 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Luxturna (voretigene neparvovec) 5×10^{12} vg/mL, concentrated subretinal solution for injection for the following proposed 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 mutation who have sufficient viable retinal cells.*

Inherited retinal dystrophies (IRD) are a broad range of genetic retinal disorders associated with progressive visual dysfunction caused by mutations in any one of over 220 different genes.

The *RPE65* gene codes for the retinal pigment epithelium 65kDa protein (RPE65) also known as all-transretinyl isomerase, which catalyses the regeneration of 11-cis-retinal. This process is an essential part of the retinoid cycle for the biological conversion of light energy to electrical signalling by retinal photoreceptors. Biallelic *RPE65* mutations lead to the absence of the functional RPE65 enzyme, resulting in accumulation of toxic precursors and damage to the retinal pigment epithelium, which in turn leads to damage of the photoreceptors that depend on the retinal pigment epithelium (RPE) cellular metabolism.

RPE65 enzyme deficiency mainly affects rod photoreceptors that mediate peripheral vision, and the ability to detect and see in low luminance light. Cone photoreceptors are regulated by a different biochemical pathway and are secondarily affected in these individuals. As a result of rod-mediated degeneration, affected individuals have such

decreased light sensitivity that they are night blind and have difficulty performing daily living activities, even under normal daytime lighting conditions. Continued retinal degeneration inevitably includes cone photoreceptors as well, and eventually progresses to near total blindness in almost all patients.

Depending on time of onset, severity, and presenting phenotype, individuals with IRD due to autosomal recessive mutations in *RPE65* may have different clinical presentations resulting from a common cause of reduced or absent levels of RPE65 enzyme. Common presentations include what would have previously been described as Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP). There is considerable heterogeneity in clinical presentation amongst patients with biallelic *RPE65* mutations.

LCA is a group of autosomal recessive eye disorders that primarily affects the retina. The estimated worldwide prevalence of LCA is between 1 in 33,000 and 1 in 81,000 individuals. Based on published data, mutations in the RPE65 gene were identified in 8 to 16% of patients described as having LCA, which equates to 40 to 80 individuals in Australia. Symptoms of LCA typically become evident from 2 to 3 months of age and include progressive, profound reduction of visual acuity; concentric reduction of visual fields; night blindness; and nystagmus. Patients have great difficulty performing daily living activities, even under normal daytime lighting conditions, and most are blind by young adulthood.

RP comprises heterogeneous retinal diseases characterised by progressive degeneration of rod and cone photoreceptors. RP can have either autosomal dominant, autosomal recessive or X-linked pattern of inheritance. RP is a major cause of inherited blindness, affecting approximately 1 in 5000 people worldwide. Patients with a clinical diagnosis of RP generally have a more variable onset and slower disease progression. Symptoms include a progressive loss of night and peripheral vision and constriction of the visual field, with most patients eventually experiencing loss of visual acuity (VA) as the disease progresses. It is estimated that 1 to 3% of all patients with RP have an underlying *RPE65* mutation, equating to approximately 222 people affected by this specific mutation in Australia.

Patients with inherited retinal disorders are currently seen in specialised ophthalmology clinics in Australia. They are offered genetic testing, primarily to assist with counselling of other family members.

Regulatory status

Luxturna (voretigene neparvovec) is considered to be a new biological entity for regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in 3 jurisdictions (the European Union (EU), United States of America (USA) and Switzerland) and was under consideration in Canada, as shown in the table below.

There had been extensive consultation between Spark Therapeutics, legacy sponsors and the US Food and Drug Administration (FDA) during product development.

Table 1: International regulatory history

Region	Submission date	Status	Approved indications
European Union	29 July 2017	Approved on 22 November 2018;[2]	*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.*
United States of America	14 July 2017	Approved on 19 December 2017;[3]	*treatment of patients with confirmed biallelic RPE65 mutation associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).*
Switzerland	10 May 2019	Approved on 14 February 2020	*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.*
Canada	31 October 2019	Under consideration[4]	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

[2] The initial market authorisation holder for Luxturna was Spark Therapeutics Ireland Ltd. Novartis Europharm Ltd is the current EU market authorisation holder.
[3] Spark Therapeutics Inc is the market authorisation holder (Biologics License Application (BLA) holder) in the USA.
[4] The application was subsequently approved in Canada (Notice of Compliance issued by Health Canada on 13 October 2020).

Table 2: Timeline for Submission PM-2019-02585-1-5

Description	Date
Designation (Orphan[5])	19 March 2019
Submission dossier accepted and first round evaluation commenced	31 July 2019
First round evaluation completed	8 January 2020
Sponsor provides responses on questions raised in first round evaluation	10 March 2020
Second round evaluation completed	15 April 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	30 April 2020
Sponsor's pre-Advisory Committee response	19 May 2020
Advisory Committee meeting	5 June 2020
Registration decision (Outcome)	4 August 2020
Completion of administrative activities and registration on the ARTG	5 August 2020
Number of working days from submission dossier acceptance to registration decision*	208

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

[5] Orphan drugs are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine

Quality

The quality evaluator recommended approval.

Voretigene neparvovec employs the adeno-associated virus serotype 2 (AAV2) vector as a delivery vehicle for an expression cassette that contains a normal human *RPE65* gene. The recombinant vector is a non-enveloped icosahedral virion of approximately 26 nanometres in diameter. The parent AAV2 virus is a non-pathogenic, single-stranded DNA genome-containing, helper virus-dependent member of the parvovirus family.

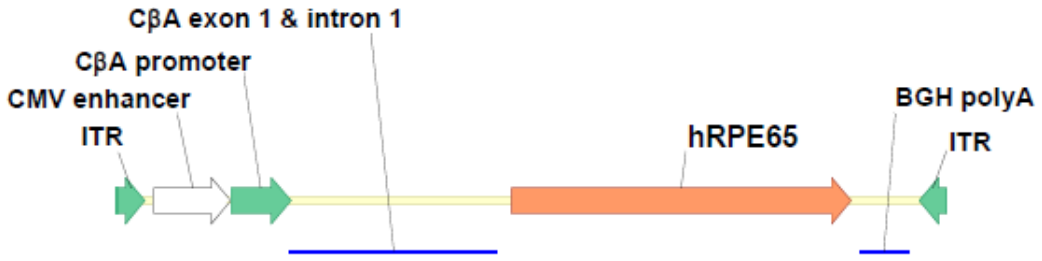
Voretigene neparvovec (AAV2-hRPE65v2);[6] was derived from the naturally-occurring AAV2, a member of the parvovirus family. Wild-type adeno-associated virus (AAV), which is ubiquitous in the environment, has not been associated with human disease. It is naturally replication deficient, requiring coinfection 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, 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 DS, the AAV2 wild-type genome containing rep and cap genes is replaced with the following components:

- the cytomegalovirus (CMV) enhancer;
- the chicken beta actin (CBA) promoter;
- the CBA exon 1 and intron;
- the cloned cDNA coding for human retinal pigment epithelium 65kDA protein (hRPE65); and
- the bovine growth hormone polyadenylation (PolyA) region.

The ITR regions, which flank the inserted genes, are retained.

Figure 1: Schematic representation of the voretigene neparvovec vector



BGH = bovine growth hormone, CβA = chicken beta actin, CMV = cytomegalovirus, ITR = inverted terminal repeat, RPE = retinal pigment epithelium.

AAV2 is produced in HEK293 cells through transient transfection with three plasmids that contain the genetic information to produce the coded viral vector. The three plasmids required for the manufacture of voretigene neparvovec are:

A vector plasmid pAAV2-hRPE65v2, a [Information redacted] plasmid encoding a human retina associated hRPE65 gene and regulatory elements; a packaging plasmid [Information redacted], and a helper plasmid [Information redacted]. The drug is manufactured in the USA and transported to Australia.

[6] **AAV2-hRPE65v2** = Adenovirus-associated viral vector serotype 2 containing the human *RPE65* gene.

Nonclinical

The nonclinical evaluator recommended approval, for the following reasons discussed in this section.

Biochemical, electroretinography, pupillometry and behavioural effects

Following subretinal injection of voretigene neparvovec or similar vectors to young *RPE65*-deficient mice and dogs; the positive biochemical, electroretinography, pupillometry and behavioural effects observed supports Luxturna use for the proposed indication. The localised and selective transduction of RPE cells resulted in expression of the RPE65 protein, recovery of the visual cycle, and recovery of visual function.

Vector biodistribution

Vector biodistribution was evaluated in the toxicology studies in dogs and monkeys. Vector DNA was primarily detected in intraocular fluids of injected eyes, with lower levels detected in the optic nerve of the vector injected eye and in the optic chiasm. In two dogs, the preauricular lymph nodes draining the bulbar conjunctiva on the injected side had positive responses for vector DNA three months after injection. In addition, in monkeys, vector DNA was detected in spleen and liver, and sporadically in the lymph nodes. Very low levels of vector were also detected in the colon, duodenum and trachea of a single high dosed monkey. Importantly, vector DNA was not detected in the gonads of either species, nor in brain, heart or lungs.

Immune response

There was no evidence of pro-inflammatory T-cell responses to the AAV2 capsid or RPE65 protein in monkeys, and a limited T-cell response to (human) RPE65 in dogs. Antibodies to RPE65 were only detected in isolated cases. Antibodies (including neutralising antibodies) to AAV2 capsid proteins were variously detected in the anterior chamber fluid or serum of both normal and RPE65-deificient dogs; monkeys did not develop anti-AAV2 antibodies after single subretinal administration of voretigene neparvovec.

Toxicity studies

The toxicity of subretinally administered voretigene neparvovec was examined in single- and repeat-dose studies in dogs (normal and RPE65-deficient) and monkeys. Single-dose studies with an earlier version of the vector (yielding limited protein expression) were additionally performed in dogs. Follow-up periods ranged from three weeks to two years. Repeat dosage studies involved a second administration to either the contralateral eye or to the initial eye again. Doses of voretigene neparvovec tested in animals were up to 5.5 times the clinical dose in dogs; and five times in monkeys respectively. The earlier version of the vector was given to dogs at ten times the human dose.

The main findings in the toxicity program were inflammatory responses at the injection site and trauma relating to the injection procedure.

The only extraocular findings were minimal perivascular lymphocyte cuffing in the brainstem and midbrain; minimal mixed perivascular infiltration of the choroid plexus; and mild optic nerve lesions in 25% of the dogs who were administered the earlier version of the vector at 1.5×10^{12} vg per eye. This may reflect an immune response following vector leakage by reflux into the vitreous chamber, leading to ganglion cell exposure. This is unlikely to be relevant to human where a ten-fold lower dose is used and a more refined surgical procedure is employed. In addition, the gene administered to dogs is not identical

to the gene coding for a similar protein, and the animals did not receive pre-treatment with prednisolone.

Although no genotoxicity or carcinogenicity studies have been conducted, based on published literature,[7] the risk of insertional mutagenesis and carcinogenicity with a vector of this type is considered to be low.

No reproductive and developmental toxicity studies with voretigene neparvovec have been performed. This was considered acceptable given the nature of the product and from the absence of biodistribution to the gonads. Assignment to Pregnancy Category B2;[8] was recommended.

Clinical

Contents of the clinical dossier

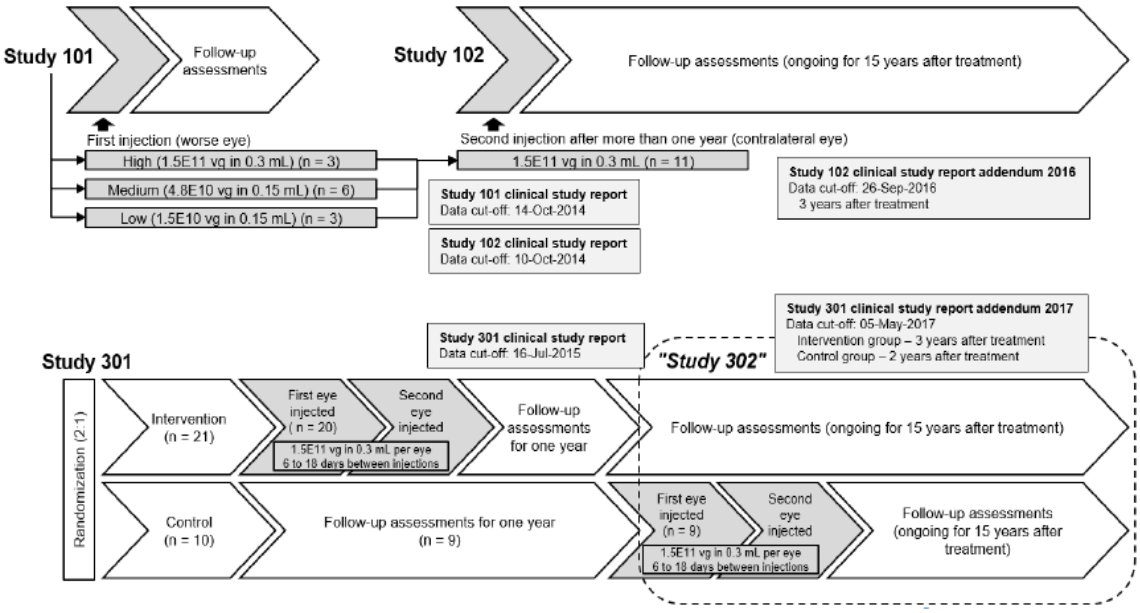
The clinical evaluation contained the following components:

- Study AAV2-hRPE65v2-301 (Study 301), a Phase III study with 3 addenda, considered as the pivotal study;
- StudyAAV2-hRPE65v2-101 (Study 101), a Phase I study;
- Study AAV2-hRPE65v2-102 (Study 102), a Phase I study with 2 addenda;
- Study MTVS, a mobility testing validation study (prospective observational study to support the use of multi-luminance mobility testing (MLMT) as the primary efficacy endpoint for Study 301);
- Study RPE65 NHx, a retrospective natural history study;
- periodic safety update reports (PSUR) covering the reporting period of 19 December 2017to 24 January 2019; and
- multiple literature references.

[7] Bozanić D. and Saraga-Babić M. Cell proliferation during the early stages of human eye development. *Anat. Embryol.* 2004; 208: 381–388.

[8] The Australian categorisation system for prescribing medicines in pregnancy states that for Category B2: 'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.'

Figure 2: Clinical programme overview



Overall there were 41 subjects who received voretigene neparvovec as part of the clinical development programme, with all subjects having a molecular diagnosis of biallelic *RPE65* mutation by a certified laboratory. There were 34 unique *RPE65* mutations among the 41 subjects in the development programme; both compound heterozygotes and homozygotes were included.

Subjects participating in Studies 301, 101 and 102 were transferred to the long-term follow-up Study AAV2-hRPE65v2-LTFU-01, which will evaluate safety and efficacy outcomes annually for a total period of 15 years.

Efficacy

Study AAV2-hRPE65v2-301

Study AAV2-hRPE65v2-301 (also referred to as Study 301) was a Phase III, open-label, randomised, controlled study to assess the safety and efficacy of AAV2-hRPE65v2 (voretigene neparvovec) in subjects with LCA due to *RPE65* mutations.

The primary objective of the study was to determine whether non-simultaneous, bilateral sub-retinal administration of AAV2-hRPE65v2 improves the ability to navigate (as measured by standardised mobility testing) in adults and children aged 3 years and older with *RPE65* mutations.

Subjects randomised to the intervention group (n = 21) received a dose of 1.5 x 10^{11} vg of AAV2-hRPE65v2 in each eye. Subjects in the control group did not receive any treatment for at least 12 months. Following retinal and visual assessments at 12 months, subjects in the control group still meeting eligibility criteria were crossed over to receive non-simultaneous bilateral (within 6 to 18 days) sub-retinal injections of 1.5 x 10^{11} vg of AAV2-hRPE65v2 as per the intervention group. This part of the study is referred to by the sponsor as 'Study 302'.

Efficacy assessments were conducted at Days 30, 90, 180 and 1 year following the second vector administration procedure with the primary efficacy analysis at Year 1. The study was conducted at two centres in the USA.

Eligible participants were male and female subjects aged 3 years and older with IRD due to *RPE65* mutations;[9] with best-corrected visual acuity worse than 20/60 in both eyes, and/or visual field less than 20 degrees in any meridian as measured by visual field score of Goldmann III4e isopter or equivalent;[10] in both eyes. The sponsor did not consider the subgrouping of patients using historical labels such as LCA or RP to be as important as a genetic diagnosis in defining patients eligible for treatment. Subjects were to have sufficient viable retinal cells as determined by non-invasive means (such as optical coherence tomography (OCT) and/or ophthalmoscopy). This was defined as either:

- an area of retina within the posterior pole of greater than 100 μm thickness shown on OCT;
- greater than or equal to three disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or
- remaining visual field within 30˚ of fixation as measured by Goldmann III4e isopter or equivalent.[10]

Procedure technique

Delivery of AAV2-hRPE65v2 used a standardised procedure. It comprised of a standard 3-port pars plana vitrectomy and subretinal injection of AAV2-hRPE65v2. Two surgeons are required to perform this procedure. Surgery was performed under general anaesthesia supplemented by retrobulbar block. The eye was prepped with 5% betadine solution placed in the conjunctival fornix and on the periocular skin, and draped under sterile conditions. AAV2-hRPE65v2 was administered using a commercially available cannula designed for subretinal injection.[11]The extent of the injection included a portion of the macular area, but avoiding the vicinity of the fovea. The cannula tip was placed on the retina in the area of the papillomacular bundle, superotemporal to the optic nerve and superior to the macular centre. The cannula was placed a minimum of 2 mm from the foveal centre but posterior to the equator of the eye. Ocular corticosteroids and antibiotics were used during the procedure. They were retrobulbar infusion of 1 mL triamcinolone acetonide solution (40 mg/mL), subconjunctival injection of 0.5 mL of dexamethasone solution (4 mg/mL) and 0.5 mL vancomycin (50 mg/mL); or 0.5 mL cefazolin sodium (100 mg/mL) antibiotic solution. The ocular surface was dressed with prednisolone acetate 0.6%/gentamicin sulfate 0.3%; or tobramycin 0.3%/dexamethasone 0.1% ointment.

Systemic corticosteroids were administered for 18 to 30 days inclusive, depending on the timing of the second injection, to minimise inflammation associated with the surgical procedure and to reduce the potential for an immune response to the AAV2-hRPE65v2 capsid and transgene product. Subjects received oral prednisone at a dose of 1 mg/kg/day (maximum 40 mg/day) commencing 3 days prior to the first administration of AAV2-hRPE65v2, for a total of 7 days followed by a tapering course, which was 0.5 mg/kg/day for 5 days, then 0.5 mg/kg/every other day for 5 days. The prednisone regimen was repeated for the second injection, with this regimen superseding the tapering of the regimen following the first injection.

Endpoints

The primary efficacy endpoint was bilateral performance on the standardised multi-luminance mobility test (MLMT), as measured by the mean change from Baseline to Year 1. The MLMT was developed by the sponsor to capture the specific functional defect caused by this disorder. It comprised 12 different mobility courses printed on heavy white

[9] The patients' molecular diagnosis were performed or confirmed by CLIA-certified laboratory.
[10] The **Goldman Visual Field Kinetic Perimetry Test** measures visual sensitivity in a given location. Each isopter indicates the size of the visual stimulus and its light attenuation.
[11] Bausch and Lomb Storz Retinal Cannula (REF E7365)

cloth with the path indicated by printed black arrows standardised to dimensions consistent with Snellen lettering for VA of 20/200 at 2 metres. The mobility course was 5 feet by 10 feet in size with a one foot border. Each course included standardised number of arrows, turns and obstacles. There were 7 specified luminance levels: 1, 4, 10, 50, 125, 250 and 400 lux corresponding to poorly lit sidewalk at night (1 lux) to studio with floodlights (400 lux). Subjects were tested from dimmest to brightest light.[12]

A change score of 1 was considered a clinically meaningful change based upon advice from physicians familiar with these patients and the MTVS study.

The secondary endpoints of the study were:

- full-field light sensitivity threshold (FST) testing: change from Baseline to Year 1 in average light sensitivity for white light (averaged over both eyes);
- monocular mobility testing change score: change from Baseline to Year 1 in the score of the mobility testing for the first eye; and
- visual acuity (VA): average change in VA from Baseline to Year 1 (averaged over both eyes).

Exploratory endpoints included visual field (VF) testing (Humphrey and Goldmann), visual function questionnaire, pupillary light reflex testing, contrast sensitivity and independent orientation and mobility assessments.

Results

There were 36 subjects screened and 31 subjects randomised (n = 21 to intervention and n = 10 to control). Overall 29 subjects (n = 20 intervention, n = 9 control) completed the Year 1 assessment. Two subjects discontinued the study on the day of randomisation prior to any intervention.

There were 21 subjects in the intervention group and 10 subjects in the control group. The mean age was 15.1 years (range 4 to44 years). Nystagmus was present for all subjects except one in the intervention group. The mean VA at Baseline was 1.18 logMAR in the intervention group (range 0.72 to 2.17), and 1.29 in the control group (range 0.51 to 4);[13,14] The mean and standard deviation (SD) FST score for white light was -1.29 (0.09) and -1.65 (0.14) $\log_{10}$ candela second per metre squared ($cd.s/m^2$) in the intervention and control group respectively at Baseline. The lowest lux level at which subjects in the intervention group passed the MLMT at Baseline ranged from 4 to greater than 400 lux, with the majority of subjects passing the test bilaterally at less than 125 lux. There were two (10%) subjects in the intervention group and one (10%) subject in the control group who did not pass the test at 400 lux, and were assigned a lux level of greater than 400.

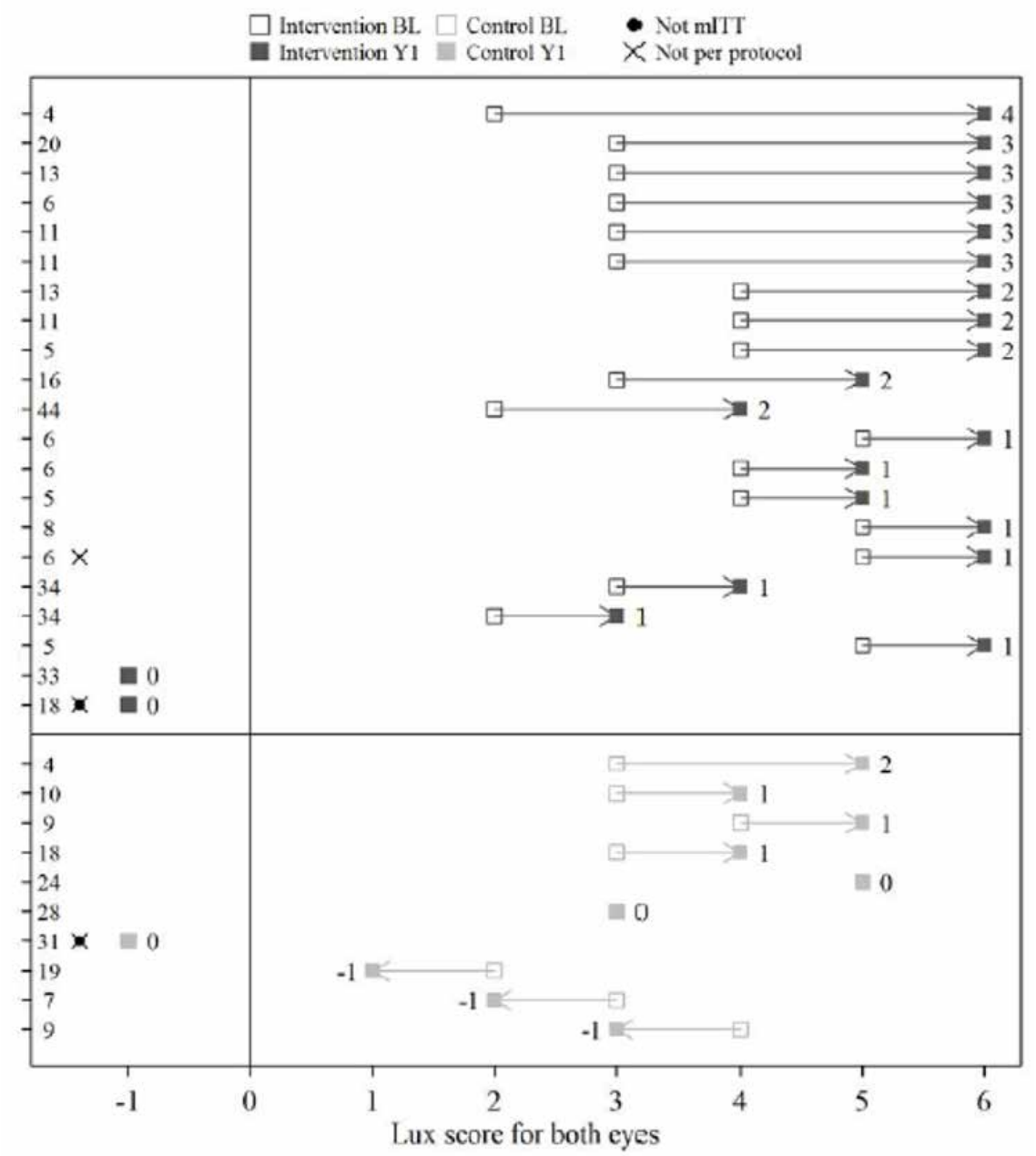
[12] Sponsor clarification: The testing of each subject was recorded (both video and audio) and assessed by independent masked graders. Each lux level is represented by a lux score. The change score metric is the change in lux score as compared to Baseline. A positive change score reflects passing the MLMT at a lower light level (or higher lux score) than at Baseline. A lux score of 6 (passing the course at the 1 lux level) reflects the maximum possible MLMT execution for a given visit.

[13] A **LogMAR** is a notation of vision loss and refers to the scoring of visual acuity with reference to **logarithms of the minimum angle of resolution** using a LogMAR chart, also known as an ETDRS (Early Treatment Diabetic Retinopathy Study) chart. A LogMAR chart consists of rows of letters and is used by ophthalmologists, orthoptists, optometrists, and vision scientists to estimate visual acuity, particularly in the field of research. An observer who can resolve details as small as 1 minute of visual angle scores LogMAR 0, since the base-10 logarithm of 1 is 0; 0 LogMAR indicates standard vision (equivalent to 20/20 on the Snellen chart). An observer who can resolve details as small as 2 minutes of visual angle (that is, reduced acuity) scores LogMAR 0.3, since the base-10 logarithm of 2 is near-approximately 0.3; and so on. Positive values indicates poor vision, and negative values indicates good vision.

[14] Note that 0.5 logMAR is equivalent to 20/63, 1.1 to 20/250. Blindness is defined as a best correct vision at worse than 1.3 logMAR.

The mean and SD bilateral MLMT change score for Year 1 compared to Baseline was 1.8 (1.1) and 0.2 (1.0) for the intervention and control groups respectively; with a mean difference (intervention versus control) of 1.6 (95% confidence interval (CI): 0.72, 2.41; p = 0.001). The median MLMT change score was 2 in the intervention group and 0 in the control group.

Figure 3: Study AAV2-hRPE65v2-301 Bilateral multi-luminance mobility test scores at Baseline and Year 1 by individual (intention to treat population)



BL = Baseline, Y1 = Year 1, mITT = modified intention to treat group.

The ages of patients at randomisation are displayed at the leftmost section of graph next to each Subject ID [subject IDs redacted]; the Lux change scores are displayed next to the Year 1 Lux score.

The sponsor stated a minimal clinically important difference (MCID) in Lux score was 1, however the figure above demonstrates a variability of +/- 1 in the control group. The improvement in Lux score was noticed at Day 30 and persisted until 1 year. Eleven out of 21 subjects in the treatment group had an improvement in 2 Lux scores or more; one out

of 10 subjects in the control group had an improvement of 2 Lux scores. No patient in the intervention group deteriorated. Two patients in the treatment group had no response.

The mean and standard error of the mean (SE) change across both eyes for FST from Baseline to Year 1 was -2.08 (0.29) $\log_{10}(cd.s/m^2)$ and 0.04 (0.44) $\log_{10}(cd.s/m^2)$ for the intervention and control groups respectively, with a mean treatment difference (intervention versus control) of -2.11 $\log_{10}(cd.s/m^2)$ (95% CI: -3.19, -1.04; $p < 0.001$). This represents a 100 fold improvement in light sensitivity and is above what is considered clinically meaningful.

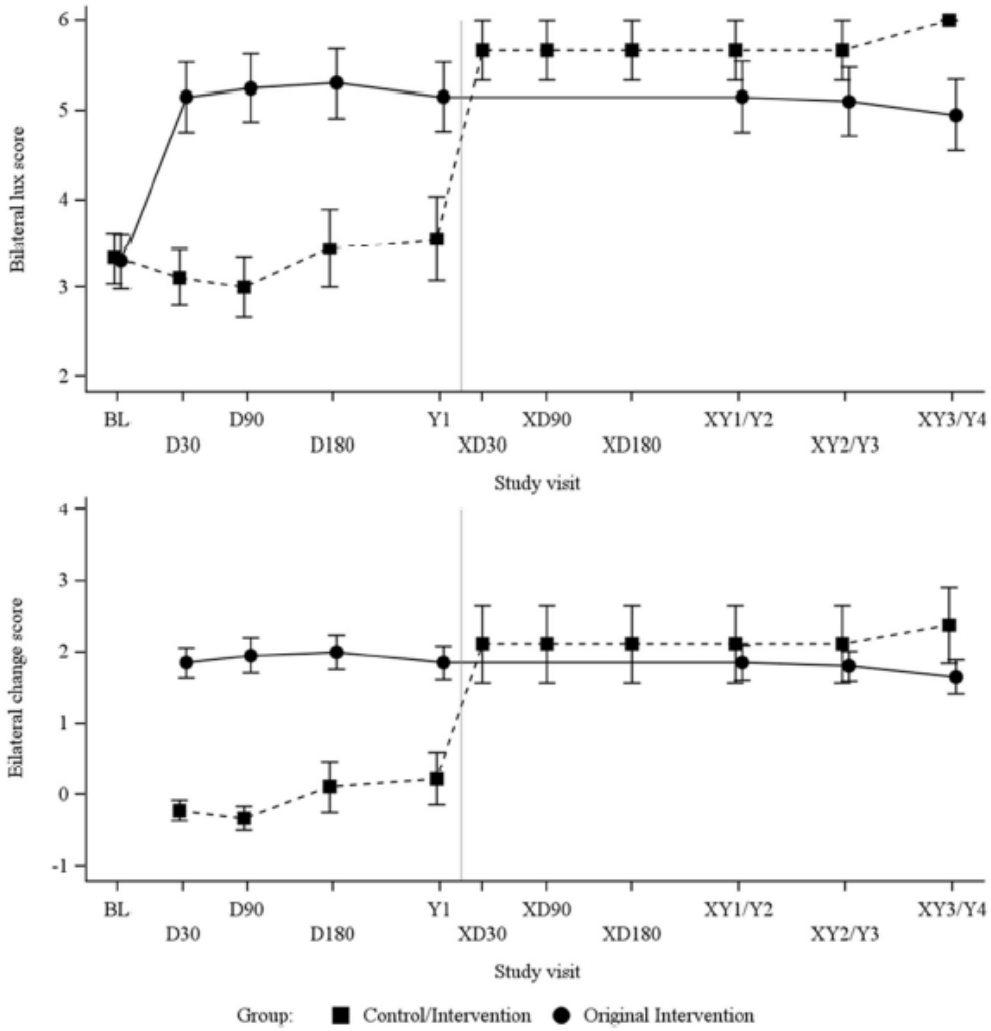
In relation to exploratory endpoints, there was an improvement in the visual function questionnaire in the intervention group but not the control group.

Long term efficacy

The dossier included efficacy data through to 2 July 2018. This included year 4 data for 20 subjects in the original intervention group and Year 3 data for 8 subjects in the control/intervention group.

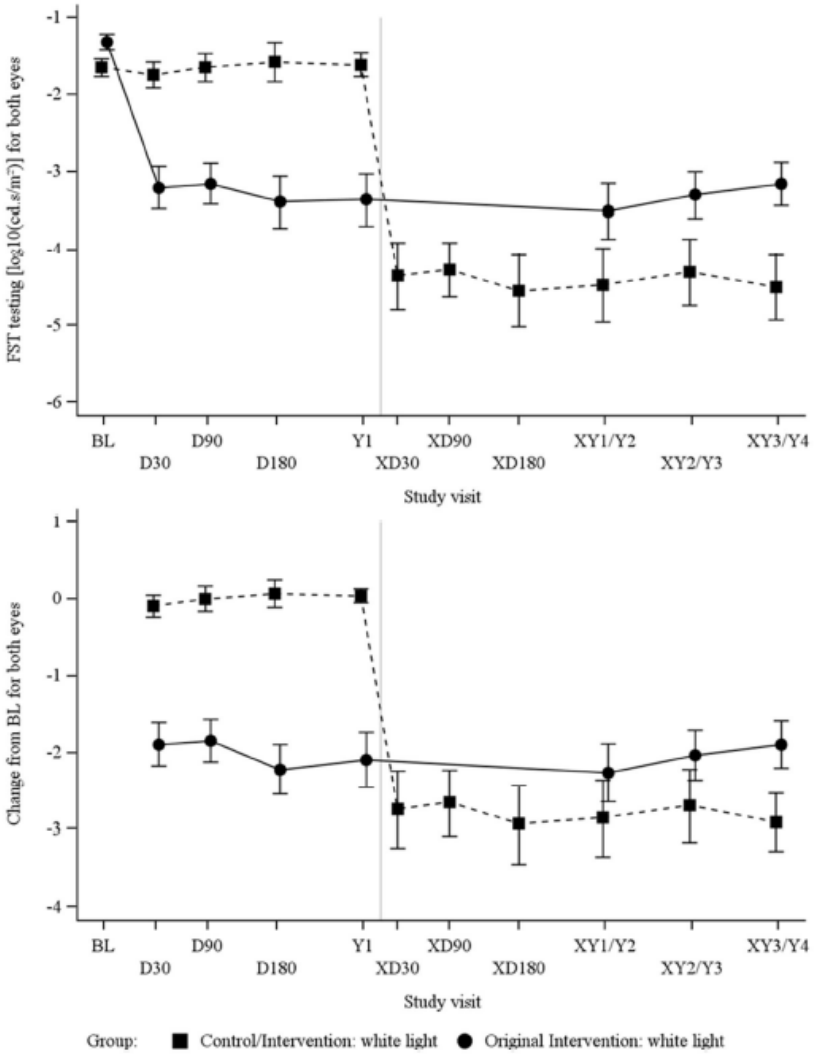
For subjects in the original intervention group, the mean and SD bilateral MLMT change score from injection Baseline was 1.9 (1.1), 1.8 (1.0) and 1.7 (1.1) at Year 2, Year 3 and Year 4 respectively. For subjects in the control/intervention group, the mean and SD bilateral MLMT change score from injection Baseline was 2.1 (1.6) at Year 2 and 2.4 (1.5) at Year 3.

Figure 4: Study AAV-hRPE65v2-301 Bilateral mobility testing scores, means over time (modified intention to treat population/ safety population)



BL = Baseline. MT = mobility testing. D = Day. Y = Year. X = crossover. Intervals are ± standard error of the mean (SE).

Figure 5: Study AAV-hRPE65v2-301 Full field light sensitivity threshold with white light, observed means over time for both eyes (modified intention to treat population/ safety population)



BL = Baseline. cd.s/m^2 = candela second per meter squared. FST = full-field light sensitivity threshold. SE = standard error. X = cross over. Data presented as mean ± SE. For control/intervention, change is relative to injection Baseline after Year 1.

Safety

The dossier contained a consolidated safety analysis across all clinical studies (data cut off May 2017). This included at least 3 years of follow up from Study 301, and 2 years of follow up from Study 302. Studies 101 and 102 provided at least 7 years of cumulative data and 4 years of data following administration of voretigene neparvovec to the second eye for subjects in Study 102.

Overall, 41 subjects and 81 eyes have received subretinal injections of voretigene neparvovec across Phase I and Phase III studies. There was no placebo or control group.

The most common treatment emergent adverse events (TEAE) by Preferred Term were: headache (n = 21; 51%), leucocytosis (n = 17; 41%), pyrexia (n = 17; 41%), nasopharyngitis (n = 16; 39%), nausea (n = 14; 34%), cough (n = 13; 32%), vomiting (n = 13; 32%) and oropharyngeal pain (n = 11; 27%).

At the time of data cut off there were 17 (41%) subjects reporting 29 ongoing TEAEs, most commonly cataract (9 eyes in 5 subjects). Fourteen of the ongoing events were considered to be related to the administration procedure (most frequently cataract, followed by maculopathy) and none considered related to the vector.

Ocular TEAEs were considered adverse events of special interest and included events reported in the MedDRA;[15]System Organ Class (SOC) of 'Eye Disorders' and particular TEAEs in the SOCs 'Infections and Infestations' and 'Injury, Poisoning and Procedural Complications'. There were 30 (73%) subjects with ocular TEAEs at the time of data cut off. The most common ocular TEAEs across the clinical studies were: conjunctival hyperaemia (n = 9; 22%), cataract (n = 9; 22%), increased intraocular pressure (n = 8; 20%), retinal tear (n = 4; 10%) and eye pain (n = 4; 10%). The majority of ocular events were related to the administration procedure, with three events of retinal deposit considered to be related to the vector. Retinal deposits were transient.

Cataracts are a known complication of IRD. Retinal tears were repaired with laserpexy during the vector administration procedure and all resolved without sequelae.

Serious adverse effects considered related to the administration procedure were reported for 3 of 41 subjects (7%); n = 1 (2%) each with retinal disorder (loss of foveal function), retinal detachment and increased intraocular pressure resulting in optic atrophy (secondary to administration of depot-corticosteroid given to treat endophthalmitis related to the administration procedure).

Vector shedding

Vector shedding was measured by quantitative polymerase chain reaction to detect AAV2 vector DNA containing the *RPE65*-transgene. Samples were taken from tears and blood. There were 14 of 29 (48%) of subjects in the modified ITT/safety population of studies 301/302 with positive tear and or serum samples; n = 9(45%) in the original intervention group and n = 5(56%) in the control/intervention group. Overall, vector genome was detected in tears for 13 of 29 (45%) subjects. Vector DNA was not detected in any whole blood samples.

Thirteen subjects had positive tear samples; for 8 subjects samples were positive on Day 1 only. There were 5 subjects with more than one positive sample; 4 subjects were positive up to Day 3 post vector administration and 1 subject in the control/ intervention group had positive tear samples at Day 14 post vector administration. The range for copies of AAV2 hRPE65v2 per reaction was 12 to 994 copies across tear samples for Day 1 and Day 3, and 61 copies of AAV2 hRPE65v2 at Day 14 for one patient in the control/ intervention group – that are all very low number of viral DNA.

Vector genome was detected in serum samples from 3 of 29 subjects, for all subjects serum samples were positive for up to 3 days.

Cell mediated and humoral immune response to both capsid and transgene product were tracked in Studies 301 and 302 using antigen specific T cell reactivity against AAV2 capsid and RPE 65 whole protein in peripheral blood mononuclear cells. Samples were analysed with ELISpot assays to detect interferon gamma through quantification of 'spot forming units' and concentrations of Immunoglobulin G antibodies against AAV2 capsid in serum

[15] The **Medical Dictionary for Regulatory Activities** (**MedDRA**) is a single standardised international medical terminology, developed as a project of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (that is, from clinical trials to post-marketing surveillance). Furthermore, MedDRA supports ICH electronic communication within the ICH's Electronic Common Technical Document (eCTD) and the E2B Individual Case Safety Report.

samples were analysed using a validated enzyme-linked immunosorbent assay (ELISA) method.

In Study 301, interferon gamma (IFN-γ) ELISpot assay results for AAV2 capsid and RPE65 were negative at the time points evaluated, with the exception of 3 subjects with a positive response at a single time point, against either RPE65 or AAV2 capsid, not both simultaneously. In Study 302, five subjects in the control/intervention group showed a positive IFN-γ ELISpot assay result and four subjects had a positive response to RPE65.

There was a variable response in immunoglobulin G antibodies; some patients had no response, others a small transient increase. There was no clinical correlation with these responses.

Risk management plan

The following risk management plan versions were submitted and evaluated:

- European Union-RMP version 1.5 (dated 4 October 2018; Data lock point 5 May 2017)
- Australian Specific Annex version 1.0 (dated 13 June 2019)
- Updated version Australian Specific Annex 2.0 (dated 26 February 2020).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3.[16]

Table 3: Risk Management Plan for Luxturna

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important Identified Risks	Increased intraocular pressure	ü	ü	ü	ü*
	Retinal tear	ü	ü	ü	ü*
	Macular disorders	ü	ü	ü	ü*
	cataract	ü	ü	ü	ü*
	Intraocular inflammation and/or infection related to the procedure	ü	ü	ü	ü*
	Retinal detachment	ü	ü	ü	ü*

[16] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the Product Information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	Tumorigenicity	ü	ü	–	–
	Host immune response	ü	ü	ü	–
	Third party transmission	ü	ü	ü	–
Missing information	Long term efficacy (> 4 years)	ü	ü	–	–
	Use in pregnancy and lactation	ü	ü	ü	–
	Use in children < 3 years of age	ü	ü	ü	–
	Long term safety (> 9 years)	ü	ü	–	–

Additional pharmacovigilance includes ongoing long-term follow-up study to address all safety concerns and a proposed European Union patient registry to address all but long-term safety (> 9 years). Australian patients will be included in this registry.

* Additional risk minimisation measures include patient alert card, patient leaflet and Healthcare Professional education.

- The summary of safety concerns is acceptable from an RMP perspective at the first round of evaluation.
- A patient registry is planned to be conducted in the EU. The sponsor states that Australian patients will be included in the EU registry.
- The RMP evaluator has requested more information from the sponsor with regards to the risk minimisation plan in order to evaluate its acceptability. The sponsor should provide the Surgical and Pharmacy manuals, patient alert card and the patient leaflet intended for Australia to the TGA for approval prior to implementation.
- There are ongoing studies:
  - 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. The final report is due in 2031.
  - SPKRPE-EUPASS is a single group, prospective, observational, multi-centre (in ocular gene therapy centres and inherited retinal dystrophy referral sites) registry designed to collect data on long term safety outcomes in patients treated with voretigene neparvovec. The final report is due in June 2030.

Risk-benefit analysis

Delegate's considerations

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.*

Several aspects of this indication require further discussion.

Firstly, treatment of paediatric and adult patients is proposed. As this is an inherited disorder and may present in infancy or childhood, once all currently diagnosed patients are treated in Australia the treatment will most likely involve primarily children. In the clinical studies, the youngest child was 4 years old. Although efficacy in younger children with the genetic mutation could be extrapolated from the data, the dose required and optimal surgical technique is not established.

Second the term 'vision loss' in the indication is ill defined. The criteria for enrolment included best corrected visual acuity of 20/60 or worse with both eyes, and/or a visual field less than 20 degrees meridian. In addition they must have been unable to pass mobility testing at 1 lux. The clinical studies included patients with a range of disease severity. The study did not examine whether this treatment is helpful to prevent vision deteriorating in patients without 'vision loss'.

Thirdly 'sufficient viable retinal cells' was defined in the clinical studies as either 'an area of retina within the posterior pole of greater than 100 μm thickness as shown on OCT'; 'greater than or equal to 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole or the remaining visual field within 30 degree of fixation as measured by III4e isopter or equivalent'. The importance of sufficient viable retinal cells for Luxturna to be efficacious is highlighted by the sponsor in response to questions by the European Medicines Agency (EMA) and TGA. However, the Delegate is unsure if these methods are sufficiently robust to determine whether the cells are viable.

In the Delegate's opinion, the indication should include more specific information about patients who are eligible for treatment including:

- A description of what is meant by poor vision
- A description of what is meant by sufficient numbers of viable retinal cells.

Efficacy

As expected for a rare disease, the number of patients treated was small. The sponsor developed a novel efficacy endpoint that is sensitive for the specific visual deficits seen in the patients and relevant to patients' ability to function in the community. The problem with this is that the improvement in Lux scores may not be linear in terms of clinical significance; the test is unable to be repeated in clinical practice; and the sponsor-defined level of clinical significance of 1 Lux score is questionable as there appeared to be a variability of +/- 1 Lux in the control group.

The improvements in MLMT were mirrored by improvements in FST which is measured clinically. There was no significant improvement in visual acuity, which is expected from the disease, however it does question the significance of the improvements in Lux scores. The measures of visual fields are difficult to interpret but did appear to be in a positive direction. The quality of life questionnaire also showed an improvement.

Some patients treated with Luxturna did not respond. In response to questions from the EMA and TGA evaluator, the sponsor could not describe any readily definable factors that

may have caused this. Potential causes would include patients having insufficient viable retinal cells (despite fulfilling the defined criteria), and problems with surgical technique.

Efficacy in the real world setting may not be as great as that observed in the clinical trial as despite completing training, Australian experts would not have had the experience with this therapy as experts in the two treatment centres involved in the clinical studies.

The improvements seen in the clinical study were largely in relation to MLMT and FST; very little change was seen in VA or visual fields. It is unclear if the changes observed in the clinical trial would change a patient's functional status. In addition, as none of the criteria were used to define 'vision loss' in the indication, it is unclear if the patients' visual status actually changed.

Safety

The main adverse events seen in this study were consistent with those seen either as part of the natural history of the disease; due to prednisolone therapy; or the procedure. The retinal deposits attributable to the vector were transient and of no functional visual significance.

There was no definable pattern of immune response observed.

Shedding of the viral vector was examined in tears and blood. Loss in tears occurred for up to 14 days; in serum 3 days (in low titres). As this is a non-pathogenic non replicating virus this is not of clinical concern.

There have been cases of malignancy associated with previous gene therapies. This has not been identified so far in the clinical studies for Luxturna, and is considered unlikely due to the non-pathogenic nature of the virus.

It will be important to identify and train surgeons with expertise in this area so that the techniques involved in administering the medicine are optimised.

Comments on the risk management plan

The Delegate notes that the EU-RMP has an additional risk mitigation measure:

'*Distribution through treatment centres who have participated in the mandatory educational program on use of product and pharmacy training. Study sites/treatment centres should fulfil the following three criteria: (1) the presence of a specialist ophthalmologist with expertise in care and treatment of patients with IRDs. (2) the presence of or affiliation with a retinal surgeon experienced in subretinal surgery and capable of administrating voretigene neparvovec, (3) the presence of a clinical pharmacy capable of handling and preparing AAV vector-based gene therapy products'.*

The Delegate agrees with these requirements, however, would also add the following three criteria:

- include the involvement of a clinical geneticist in the multidisciplinary team to assist in interpretation of genetic testing;
- keep a registry of patients treated with Luxturna (or be involved in the sponsor's registry) which tracks long term efficacy and safety and can identify patients who may need alerting for future safety issues; and
- be involved in ongoing quality audits which include benchmarking of the treatment centre against other centres to ensure optimal performance.

Disposal of clinical waste and biohazards

According to the Guideline on the disposal of genetically modified organs from NSW Health, genetically modified materials should be disposed in clinical waste bins.

These are readily available in hospital settings. Other options for disposal would include a sharps bin or the pharmacy bin.

The PI states that:

> 'As a precautionary measure, patients/caregivers should be advised to handle waste material generated from dressings, tears and nasal secretion appropriately, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for 14 days after administration of Luxturna. It is recommended that patients/caregivers wear gloves for dressing changes and waste disposal, especially in case of underlying pregnancy, breastfeeding and immunodeficiency of caregivers.'

Special precautions for disposal

> 'This medicine contains genetically modified organisms. Unused medicine and waste products must be disposed of in compliance with the institutional guidelines for genetically modified organisms or biohazardous waste, as appropriate'.

These instructions in the PI appear to be appropriate. However the Delegate would recommend the term 'biohazard waste' be expanded to 'clinical biohazard waste' as there are several other categories of biohazard waste.

Furthermore, the Delegate is awaiting advice from the Office of the Gene Technology Regulator (OGTR) of the Australian Federal Department of Health, in relation to this issue.

Proposed action

Overall, the data submitted was adequate to support the quality, safety and efficacy of this product. However, the Delegate has a number of questions for the sponsor and the Advisory Committee of Medicines (ACM) around ensuring the correct patient selection for treatment; clarifying the significance of the efficacy outcomes; identifying relevant parameters to monitor in clinical practice; and ensuring there is a process of ongoing re-evaluation of efficacy and safety at each treatment centre.

The Delegate has no reason to say, at this time, that the application for Luxturna should not be approved for registration.

Questions for sponsor

The sponsor provided the following information in response to questions from the Delegate.

1. ***Please comment on how many patients in the clinical study were considered to be legally blind at Baseline, and how this changed as a result of treatment with Luxturna***

In Australia, the definition of legal blindness, as established by the Australian Government for the purposes of determining permanent blindness for Disability Support Pension or Age Pension – Blind under Section 95 of the Social Security Act 1991 (Australian Government 2006), is as follows:

> 'Visual acuity on the Snellen scale after correction by suitable lenses must be less than 6/60 in both eyes; or constriction to within 10 degrees of fixation in the better eye irrespective of corrected visual acuity; or a combination of visual defects resulting in the same degree of visual impairment as that occurring in the above points.'

For the assessments of visual function performed in the voretigene neparvovec clinical study (Study 301), these criteria would translate to:

- Visual acuity of greater than 1.0 logMAR in both the left eye and the right eye, or
- Goldman visual fields (III4e test) sum total degrees for each meridian less than or equal to 240 degrees in either eye (i.e., less than or equal to 10 degrees in each of the 24 meridians assessed in either eye).

Using these criteria, the proportion of subjects in the pivotal study 301 who were considered legally blind during the study decreased from 72.4% at Baseline to 37.9% one year after treatment (Table 2). This reduction was maintained out to four years, based on the 22 subjects who have completed the 4 year assessments.

Table 4: Study AAV2-hRPE65v2-301 Proportion of subjects meeting the criteria for legal blindness in Australia

	Study 301 subjects (n=29)*
Baseline	21/29 (72.4%)
1 year after treatment	11/29 (37.9%)
2 years after treatment	11/29 (37.9%)
3 years after treatment	11/28 (39.3%)
4 years after treatment	9/22 (40.9%)

(*) = number (percentage) of subjects meeting the criteria for legal blindness as a proportion of the number of subjects remaining in the study at the given time point.

This *post hoc* analysis showed that voretigene neparvovec treatment halved the proportion of subjects who were considered legally blind, with this benefit persisting out to at least 4 years after treatment. This finding is aligned with the improvements in functional vision and visual function observed in the study, and is in contrast to the progressive nature of inherited retinal degenerative conditions, in which patients face an inexorable deterioration of retinal and visual function, which progresses until no useful vision remains.

2. Please comment on the methods used to determine viable retinal cells. How accurate are these methods?

In the clinical study, subjects were only enrolled if they were judged by the investigators to have sufficient viable retinal cells, as determined by non-invasive means, such as OCT and/or ophthalmoscopy. The exact criteria were that subjects must have had either:

- An area of retina within the posterior pole of greater than 100 µm thickness shown on OCT, or
- Greater than 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole, or
- Remaining visual field within 30° of fixation as measured by III4e isopter or equivalent.

The methods used in the clinical study to determine viable retinal cells assessed structural (that is OCT and fundus appearance) or functional (that is visual field function) parameters. Although these are standard and commonly performed ophthalmological examination methods, there are limitations with both these methods in assessing cell viability. Anatomic assessments may not determine if the tissue is actually viable, while the functional assessment may not reflect viable but poorly functioning photoreceptors. Nonetheless, these assessments were necessary in the clinical study to minimise the

chance of enrolling any study subject with end-stage disease, who may not have provided any meaningful data on the potential benefits of voretigene neparvovec during its evaluation in the clinical program.

Although these clearly defined criteria were necessary for standardising the subject population in the clinical study, they are not optimal in real-world clinical practice, where the treating physician is best placed to determine if the patient has sufficient viable retinal cells to justify therapy. Experienced ophthalmologists in specialist centres can take a holistic view of the clinical and social aspects of the patient to have an informed discussion with the patient on the appropriateness of the treatment.

Furthermore, as technology is moving rapidly in the field of ophthalmology, the treating physician can use the most appropriate examinations to guide their treatment decision. This is in line with the opinions of the EMA and FDA assessments (Luxturna EPAR 2018;[17] Luxturna US Prescribing Information;[18]).

In addition, the sponsor believes that the revised Clinical Trials section of the Product Information (PI) better characterises the patient population that was included in the pivotal study supporting registration.

3. In section 5.3 of the ASA, it is stated that 'voretigene neparvovec will only be supplied to centres who meet the defined RMP eligibility criteria as assessed by the Australian Department of Health…' Please clarify which agency in the Department of Health that this refers to.

The sponsor wishes to clarify that the treatment centres for which funding allocation by Commonwealth and State Health Departments is independent of the sponsor. However, these centres will be supplied based on their ability to meet the OGTR license conditions, which pertain to environmental issues associated with genetic products such as the transport, and disposal of genetically modified organisms, and the eligibility criteria spelt out in the proposed RMP/ASA that is being assessed by the TGA as part of this application. Compliance to the OGTR and TGA requirements will be included in the commercial agreement between the sponsor and participating sites to ensure implementation of the RMP and OGTR license conditions.

The sponsor acknowledges the TGA Delegate is agreeable to the initially proposed three RMP criteria relating to the qualifications required from the Healthcare Professionals (HCPs) involved in the administration of voretigene neparvovec in selected centres.

Furthermore, the sponsor comments below on the three additional criteria recommended by the TGA Delegate for inclusion in the Australian RMP/ASA.

- Include the involvement of a clinical geneticist in the multidisciplinary team to assist in interpretation of genetic testing

The Royal Australian and New Zealand College of Ophthalmologists (RANZCO) Clinical Practice Guidelines for the assessment and management of patients with IRDs,[19] specifically call out the requirement to have clinical geneticists involved in multi-disciplinary teams and all subsequent clinical reviews and testing. Therefore, it would be redundant to include this requirement in the RMP.

[17] EMA, European Public Assessment Report (EPAR), Luxturna (voretigene neparvovec), EMEA/CHMP/700911/2018, 20 September 2018. Available from the EMA website.
[18] FDA Prescribing Information for Luxturna (voretigene neparvovec-rzyl intraocular suspension for subretinal injection), initial US approval 2018. Available from the FDA website.
[19] Guidelines for the Assessment and Management of Patients with Inherited Retinal Degenerations (IRD), accessed from the 'The Royal Australian and New Zealand College of Ophthalmologists' website

- Keep a registry of patients treated with Luxturna (or be involved in the sponsor's registry) which tracks long term efficacy and safety and can identify patients who may need alerting for future safety issues

The sponsor confirms that patients from Australia will be eligible to participate in the post-authorisation, multicentre, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec (CLTW888A12401). The purpose of the study is to evaluate the long-term safety profile of voretigene neparvovec for 5 years post-administration in a real-world setting. The primary objective for this safety registry study is to collect adverse events, including those of special interest via the RMP, for patients treated with voretigene neparvovec. Secondary objectives of the registry include assessment of visual function over time (for example, as measured by VA, VF, and FST), and OCT. In addition, to follow pregnancy outcomes in patients (and female partners of patients) who receive voretigene neparvovec. The frequency at which patients are followed up is determined by routine clinical practice. Data sources will include medical notes, electronic medical records, and hospital discharge files documented. The TGA RMP unit has confirmed that the sponsor's proposed RMP pharmacovigilance plan, including the utilisation of the Global patient registry, is acceptable.

- Be involved in ongoing quality audits which include benchmarking of the treatment centre against other centres to ensure optimal performance

The sponsor is proposing as a quality oversight step to develop and implement a self assessment checklist for each participating treatment centre. This annual self-assessment would cover requirements of the RMP, included but not limited to training of Healthcare Professionals, and adherence to the conditions of the OGTR license, which aims to cover environmental safety risk and waste disposal of voretigene neparvovec. Details of the implementation will be included in the commercial agreement between the sponsor and participating centres. Ongoing training and accreditation is the responsibility of the treatment centre. As per the ASA included in our MAA (Market Authorisation Application to the EU), the sponsor commits to provide support to address any identified gaps upon request from the treatment centre. Additionally, the sponsor reserves the right to suspend participation of a treatment centre where any significant gaps have been identified or persist.

In conclusion, the sponsor believes that the only additional criterion that treatment centres need to fulfil to adequately manage the risk associated with the treatment of voretigene neparvovec is for Australia to commit to enrol patients in the global registry that will document long term efficacy and safety, and can identify patients who may need alerting in the event of future safety issues. The sponsor proposes to finalise the RMP to the satisfaction of the TGA RMP Unit post-ACM, including the review of the proposed self-assessment checklist for the treatment centres.

Request for Advisory Committee on Medicines advice

1. Please comment on the way in which viable retinal cells were determined in the clinical trials. Is this the optimal criteria? Is this something routinely assessed by an ophthalmologist?
2. Please comment on the clinical significance of the improvement in MLMT and FST, in particular in the context of minimal change in VA or visual fields. How would you suggest response to treatment be monitored in the real world setting?
3. Should impaired vision be part of the indication? What parameters would you recommend?
4. Please comment on the use of Luxturna in children less than 4 years.

5. Are there any potential factors that may be associated with lack of efficacy that should be monitored in the post market registry?
6. Please comment on the feasibility of the RMP recommendations for treatment centres, and the Delegate's additional suggestions.

Advisory Committee considerations[20]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

1. Please comment on the way in which viable retinal cells were determined in the clinical trials. Is this the optimal criteria? Is this something routinely assessed by an ophthalmologist?

The ACM advised that while there are several methods used to determine whether viable retinal cells are present, there is no gold standard. The viability of retinal cells is not routinely assessed by a general ophthalmologist. Normally, patients requiring assessment of an inherited retinal disorder are referred to a specialist team for review. These specialist teams use a number of tools to assess for viable retinal cells including visual acuity, visual fields, OCT, fundoscopy, full field scotopic threshold, and electrophysiology.

2. Please comment on the clinical significance of the improvement in MLMT and FST, in particular in the context of minimal change in VA or visual fields. How would you suggest response to treatment be monitored in the real world setting?

Multi-luminance Mobility Testing (MLMT) is a functional test to measure the patients visual acuity, visual field and extent of nyctalopia in environments of varying brightness. Full field scotopic threshold (FST) is an overall measure of retinal sensitivity and function. There was a clinically significant improvement in these parameters in the study. There was also an improvement in quality of life.

In a real world setting, VA and VF are threshold tests of vision. FST would provide an assessment of real world functional improvement.

The ACM recommended that response to treatment be monitored via multimodal imaging: fundus autofluorescence (FAF), OCT and functional assessments (Humphrey visual field testing and FST). These tests should be conducted on an annual basis and documented in a registry. They also noted that a quality of life questionnaire such as that used in the clinical study could also be used.

3. Should impaired vision be part of the indication? What parameters would the ACM recommend?

The ACM was of the view that impaired vision should not be included in the indication as this may preclude treatment in younger individuals or those with later onset of disease. Removal of impaired vision from the indication is also consistent with what has been approved by other major foreign regulatory agencies.

[20] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

4. Please comment on the use of Luxturna in children less than 4 years.

As retinal dystrophy often presents in early childhood, the ACM advised that the use of Luxturna in children less than 4 years of age would be advantageous as it would allow treatment before major deterioration is present. However, the ACM considered that the need for early treatment must be balanced with surgical safety and the fragility of the developing eye, and therefore did not recommend the use of Luxturna in children less than 1 year of age.

5. Are there any potential factors that may be associated with lack of efficacy that should be monitored in the post market registry?

The ACM emphasised the importance of regular visual function testing and imaging (via FAF and OCT) to monitor patient progress and gather data towards long term outcomes. Pharmacovigilance should focus on monitoring for known complications identified from clinical trial data, but also for potential complications that may not have been previously encountered with this therapy. Visual function questionnaires such as the VFQ-25 could also assist in collecting patient reported data.

The ACM requested that precise genetic variants should be captured and recorded in the post market registry as this may be helpful when considering other phenotypic information. Each patient's age at treatment should also be recorded as in the long term this may assist in determining if there is an optimal age for treatment.

6. Please comment on the feasibility of the RMP recommendations for treatment centres, and the Delegate's additional suggestions.

The ACM noted that whilst input from a clinical geneticist may be helpful in communicating the diagnosis and any potential genetic implications to patients and carers, there should be no need for involvement by a clinical geneticist or genetic pathologist beyond the medical diagnosis.

Conclusion

The ACM considered that this product had an overall positive benefit-risk profile for the indication:

> *Luxturna is indicated for the treatment of adult and paediatric patients over 1 year of age with vision loss due to inherited retinal dystrophy caused by confirmed biallelic pathogenic or likely pathogenic RPE65 variants who have sufficient viable retinal cells.*

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Luxturna (voretigene neparvovec) 5 x 10^{12} vg per mL concentrate solution for injection vial with diluent ampoule for the following indication:

> *The treatment of patients with inherited retinal dystrophy caused by pathological biallelic RPE65 mutations and who have sufficient viable retinal cells as determined by the treating physician.*
>
> *Pathological mutations of RPE65 should be confirmed by a National Association of Testing Authorities (NATA) or International Laboratory Accreditation Cooperation (ILAC) accredited laboratory.*

Specific conditions of registration applying to these goods

- Luxturna (voretigene neparvovec) is to be included in the Black Triangle Scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Luxturna must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Luxturna European Union-Risk Management Plan (EU-RMP), version 1.5, dated 4 October 2018 (data lock point 5 May 2017), with Australian specific Annex, version 2.0, dated 26 February 2020), included with submission PM-2019-02585-1-5, to be revised to the satisfaction of the TGA, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- The PI must be included with the product as a package insert.
- The treatment centres administering Luxturna should fulfil the following criteria:
  - The presence of a specialist ophthalmologist with expertise in care and treatment of patients with IRD
  - The presence of a retinal surgeon experienced in subretinal surgery and capable of administering voretigene neparvovec
  - The presence of a clinical pharmacy capable of handling and preparing AAV vector based gene therapies
  - Include a clinical geneticist in the multidisciplinary team involved in the care of patients with inherited retinal dystrophy. This condition does not stipulate that the geneticist would need to see all patients at each visit. However, it would be expected that there would be a clinical geneticist involved in the service to assist in the interpretation of tests as required, and oversee appropriate counselling.
  - Keep a registry of patients treated with Luxturna (or be involved in the sponsor's registry) which tracks long term efficacy and safety and can identify patients who may need alerting for future safety issues. This registry should include data about vision at Baseline, how viable retinal cells were determined, and genotype.
- Batch release testing and compliance with Certified Product Details (CPD):
  - All batches of Luxturna imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - The sponsor has been granted an exemption by the TGA Laboratories to conduct testing of commercial batches of Luxturna.

  This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until written notification of any variation is given.

Attachment 1. Product Information

The PI for Luxturna approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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