May 26, 2023
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Gene Therapy Product, 2. Viral Vector Product
Non-proprietary Name	Voretigene neparvovec
Brand Name	Luxturna Injection
Applicant	Novartis Pharma K.K.
Date of Application	September 30, 2022 (Application for marketing approval)

Results of Deliberation

In the meeting held on May 26, 2023, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved. The conditional and time-limited approval is not applicable to the product. The re-examination period is 10 years.

The following approval conditions must be satisfied.

Approval Conditions

1. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product until data from a certain number of patients have been accrued in order to understand the characteristics of patients using the product and to promptly collect safety and efficacy data, thereby taking necessary measures to ensure the proper use of the product.
2. The applicant is required to take necessary measures, such as disseminating the proper use guidelines prepared in cooperation with relevant academic societies, to ensure that physicians with adequate knowledge and experience in the treatment of inherited retinal dystrophy and surgeons with adequate knowledge, experience, and technique in subretinal (submacular) surgery fully understand relevant information, including results from clinical studies of the product and adverse events reported, and that the physicians and surgeons use the product in accordance with the “Indication or Performance” and “Dosage and Administration or Method of Use” at medical institutions well equipped for providing medical care for inherited retinal dystrophy.
3. The applicant is required, in order to ensure that the product is used in compliance with the regulations on Type-1 Use approved under the “Act on the Conservation and Sustainable Use of

Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003),” to take necessary measures such as announcement of the regulations on Type-1 Use.

Review Report

May 9, 2023
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following regenerative medical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Luxturna Injection
Classification	Gene Therapy Product, 2. Viral Vector Product
Non-proprietary Name	Voretigene neparvovec
Applicant	Novartis Pharma K.K.
Date of Application	September 30, 2022

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product consisting of recombinant adeno-associated virus expressing the human retinal pigment epithelial 65kDa protein (RPE65) (the primary component) and the dedicated diluent (the secondary component). The primary component is a non-replicating, recombinant adeno-associated virus serotype 2 capsid shell containing the human *RPE65* gene under the control of a cytomegalovirus enhancer and a chicken β-actin hybrid promoter. The secondary component is the dedicated diluent used for diluting the primary component prior to administration.

Application Classification (1-1) New regenerative medical product

Items Warranting Special Mention

Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 14 of 2020 [*R2 sai*]; PSEHB/MDED Notification No. 0319-1 dated March 19, 2020, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of Cellular and Tissue-based Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with biallelic *RPE65* mutation-associated inherited retinal dystrophy, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following approval conditions.

Indication or Performance

Biallelic *RPE65* mutation-associated inherited retinal dystrophy

Dosage and Administration or Method of Use

The usual dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered as a single subretinal injection in a total volume of 0.3 mL. Subretinal administration of Luxturna to each eye should be performed on separate days within a close interval, but no fewer than 6 days apart. No repeated administration of Luxturna to the same eye is allowed.

Approval Conditions

1. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product until data from a certain number of patients have been accrued in order to understand the characteristics of patients using the product and to promptly collect safety and efficacy data, thereby taking necessary measures to ensure the proper use of the product.
2. The applicant is required to take necessary measures, such as disseminating the proper use guidelines prepared in cooperation with relevant academic societies, to ensure that physicians with adequate knowledge and experience in the treatment of inherited retinal dystrophy and surgeons with adequate knowledge, experience, and technique in subretinal (submacular) surgery fully understand relevant information, including results from clinical studies of the product and adverse events reported, and that the physicians and surgeons use the product in accordance with the “Indication or Performance” and “Dosage and Administration or Method of Use” at medical institutions well equipped for providing medical care for inherited retinal dystrophy.
3. The applicant is required, in order to ensure that the product is used in compliance with the regulations on Type-1 Use approved under the “Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003),” to take necessary measures such as announcement of the regulations on Type-1 Use.

Attachment

Review Report (1)

March 15, 2023

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Luxturna Injection
Classification	Gene Therapy Product, 2. Viral Vector Product
Non-proprietary Name	Voretigene neparvovec
Applicant	Novartis Pharma K.K.
Date of Application	September 30, 2022

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product consisting of recombinant adeno-associated virus vector expressing the human RPE65 protein (the primary component) and the dedicated diluent (the secondary component). The primary component is a non-replicating, recombinant adeno-associated virus serotype 2 capsid shell containing the human *RPE65* gene under the control of a cytomegalovirus enhancer and a chicken β-actin hybrid promoter. The secondary component is the dedicated diluent used for diluting the primary component prior to administration.

Proposed Indication or Performance

Biallelic *RPE65* mutation-associated inherited retinal dystrophy

Proposed Dosage and Administration or Method of Use

The usual dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered as a single subretinal injection in a total volume of 0.3 mL. Subretinal administration of Luxturna to each eye should be performed on separate days within a close interval, with no fewer than 6 days apart.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Luxturna is a regenerative medical product containing a non-replicating, recombinant adeno-associated virus vector (AAV) carrying the human *RPE65* gene which is one of the causative genes of inherited retinal dystrophy (IRD). Luxturna is composed of an AAV serotype 2 (AAV2) capsid shell and a gene expression cassette consisting of inverted terminal repeat (ITR), cytomegalovirus (CMV) enhancer, chicken beta actin (CBA) promoter, CBA exon 1 and intron, human *RPE65* gene complementary DNA (cDNA), bovine growth hormone (BGH) PolyA, and ITR. After subretinal administration of Luxturna, AAV2 infection occurs in the retinal pigment epithelium (RPE) cells of patients, and the gene expression cassette of Luxturna remains as an episome in the nucleus, allowing for the long-term stable expression of human *RPE65* gene. Luxturna is thus expected to improve the visual function of IRD patients with biallelic *RPE65* mutation by delivering expression of normal RPE65 protein for compensation for the loss of function of *RPE65* gene, thereby restoring the visual cycle.

Luxturna was designated as an orphan regenerative medical product with the intended indication or performance for the treatment of "biallelic *RPE65* mutation-associated inherited retinal dystrophy" on March 19, 2020 (Orphan Regenerative Medical Product Designation No. 14 of 2020 [*R2 sai*]).

1.2 Development history etc.

IRD is the collective term for hereditary retinal disorders accompanied by progressive visual disorder. More than 260 causative genes, including *RPE65* gene, have so far been identified. The diagnosis of a disease has been made based on clinical symptoms and findings, and patients with biallelic *RPE65* mutations are generally diagnosed with Leber congenital amaurosis (LCA) or retinitis pigmentosa (RP). On the other hand, it has become evident that the clinical conditions, pathogenesis, and disease progression of IRD vary depending on the causative gene(s) and their combination, and a differential diagnosis based on clinical findings may become inaccurate. For this reason, in recent years, there is an increasing need to make a diagnose of IRD based on the causative gene(s) both in and outside of Japan.

Patients with IRD with biallelic *RPE65* mutations are devoid of the activity of all-*trans*-retinyl isomerase (RPE65 protein), one of the enzymes involved in the biochemical reactions (visual cycle) induced by light absorption by photoreceptor cells of the retinal membrane. RPE65 protein is an isomero-hydrolase which converts all-*trans*-retinyl ester to 11-*cis*-retinol in RPE cells. Defect of the enzyme activity causes accumulation of cytotoxic substances in the retina, resulting in the degeneration/necrosis of photoreceptor cells and other retinal cells. In patients with IRD with biallelic *RPE65* mutation, rod cells mainly responsible for peripheral and night visions are impaired, causing severe visual impairment. Clinical symptoms observed include a significant, progressive reduction in visual acuity, afferent visual field constriction, night blindness, and nystagmus. Among them, night blindness due to decreased light sensitivity is a symptom characteristic to IRD and, in an advanced state, interferes with vision-related activities of daily life even under the day-light. Persistent retinal degeneration often progresses to total blindness.

Spark Therapeutics, Inc. in the US initiated a foreign phase I study (Study 101) in September 2007, involving patients with IRD with biallelic *RPE65* mutations. Subsequently, patients enrolled in Study 101 entered the extension study (Study 102) and received Luxturna injection in the eye contralateral to that treated in Study 101. Spark also conducted a foreign phase III study (Study 301) starting in November 2012, involving patients with IRD with biallelic *RPE65* mutations.

In the US, Luxturna was approved in December 2017, based on the data from Study 301 as the pivotal study, for the following indication or performance: "LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s)."

In Europe, Luxturna was approved in November 2018, based on the data from Study 301 as the pivotal study, for the following indication or performance: "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."

In Japan, the applicant conducted a Japanese phase III study (Study A11301) starting in November 2020, involving patients with IRD with biallelic *RPE65* mutations.

The applicant has submitted the application for the marketing approval of Luxturna with Studies 301 and A11301 as the pivotal data.

2. Quality and Outline of the Review Conducted by PMDA

Luxturna is a recombinant AAV that contains AAV2 capsid protein and ITRs derived from wild-type AAV2 and carries the human *RPE65* gene. The gene expression construct transduced by Luxturna contains human *RPE65* gene expression cassette consisting of CMV-derived enhancer domain, CBA promoter domain, CBA exon 1 and intron, human RPE65 protein-coding region, and BGH poly A signal sequence, flanked by AAV2-derived ITR regions.

Luxturna has no replication capacity as a result of deletion of *rep* and *cap* genes from wild-type AAV genome. The plasmid used for the production of Luxturna is composed of 3 plasmids, i.e., Rep2/Cap2 packaging component; E2a, E4, and VA packaging component; and human *RPE65* gene expression cassette. This design intends to avoid homologous recombination leading to the production of replication-competent viruses.

2.1 Drug substance

2.1.1 Plasmids

Three plasmids (vector plasmid, packaging plasmid, and helper plasmid) are used for the production of Luxturna. The vector plasmid contains the human *RPE65* gene under the control of CMV enhancer and CBA promoter, the packaging plasmid contains the *Rep2/Cap2* gene, and the helper plasmid contains gene expression constructs each expressing E2a, E4 or VA RNA. The control parameters for each plasmid are [redacted], [redacted], [redacted], [redacted], bacterial endotoxin, [redacted]

([redacted]), [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], sterility, [redacted], [redacted], and mycoplasma.

2.1.2 Generation and control of cell substrate for production of drug substance

Human embryonic kidney 293 (HEK293) cells are used for the manufacture of the drug substance. Thus, the master cell bank (MCB) for manufacture of the drug substance was prepared from HEK293 cells (part No. [redacted], batch No. [redacted]) obtained from [redacted] of [redacted].

The characterization of the MCB for manufacture of the drug substance and of the end of production cell (EOP) and purity tests on the MCB and EOP were conducted in accordance with the ICH Q5A (R1) and Q5D guidelines. Table 1 shows tests on adventitious agents conducted. No viral or non-viral adventitious agents were detected within the range of tests conducted.

The MCB for manufacture of the drug substance is stored in [redacted]. There is no plan for regeneration of the MCB.

Table 1. Tests on MCB and EOP for adventitious agents

In vivo virus tests (mature mice, suckling mice, guinea pigs, and embryonated eggs)
In vitro virus tests[*1]
In vitro bovine virus tests (BVDV, BAV, BPV, BTV, RSV, Reo-3, and RABV [BT cells and Vero cells])
In vitro porcine virus tests (PPV, TGEV and PAV [PT-1 cells], PCV-1, and PCV-2 [PCR])
In vitro human virus tests (CMV, EBV, HAV, HBV, HCV, HHV-6, HHV-7, HHV-8, HIV-1, HIV-2, PVB19, HTLV-1, HTLV-2, HSV-1,[*2] and HSV-2[*2])
In vitro simian virus tests (SFV,[*3] SRV,[*3] STLV,[*3] and SV40)
AAV (type 1, 2, 3, 3B, 4, and 6) test*[2]
Electron microscopy
Test for reverse transcriptase activity
Test for mycobacteria[*2]
Sterility test[*3]
Test for mycoplasma

*1 Indicator cells used were Vero cells, MRC-5 cells, and HeLa cells for MCB; and Vero cells, MRC-5 cells, and HEK293 cells for EOP.
*2 Conducted for EOP only.
*3 Conducted for MCB only.

2.1.3 Manufacturing process

The drug substance manufacturing process consists of culture expansion of the MCB ([redacted]),cell culture expansion ([redacted]), transfection, [redacted], harvesting, [redacted], [redacted] and [redacted], [redacted] and [redacted], [redacted], [redacted], preparation of bulk drug substance, filtration, and storage/test.

[redacted] are defined as the critical steps.

The manufacturing process for the drug substance has been validated on a commercial production scale.

2.1.4 Safety evaluation of adventitious agents

Table 2 shows the raw materials of biological origin other than HEK293 cells used in the drug substance manufacturing process. Both fetal bovine serum (FBS) (2) and casamino acids have been demonstrated to meet the Standards for Biological Ingredients.

Table 2. Raw materials of biological origin other than HEK293 cells

Raw material	Animal species	Material used	Process
FBS (1)	Bovine	Blood	Preparation of [redacted]
Trypsin	Porcine	Pancreas	Preparation of [redacted]
FBS (2)	Bovine	Blood	[redacted]
Casamino acids	Bovine	Milk	[redacted]

FBS (1) used for the preparation of [redacted] is derived from healthy bovine blood sourced from the US. The manufacturing process of FBS does not include assessment of viral inactivation/removal but includes filtration process for removal of pathogens. In addition, the following tests are performed: testing for viral contamination, bacterial endotoxin testing, sterility testing, and testing for mycoplasma contamination. Testing for detection of bovine viruses was performed on [redacted] prepared by using the FBS, as shown in [redacted]. No bovine viruses were detected. Although the raw material blood had been collected before 2013, the year when the US was recognized by the World Organization for Animal Health as a country of negligible risk for transmission of bovine spongiform encephalopathy (BSE) pathogens, it has been confirmed to meet a threshold for ensuring a certain level of safety against the risk of BSE by the assessment according to the notification titled “Handling of Risk Assessment, etc. in Partial Change Applications for Pharmaceuticals, Medical Devices, etc. Using Bovine-derived Raw Materials [in Japanese]” (PFSB/ELD Notification No. 0801001 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW and PFSB/SD Notification No. 0801001 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 1, 2003).

Trypsin is derived from porcine spleen sourced from the US or Canada. Although it is unclear whether the trypsin is derived from healthy animals, the material was subjected to testing for viral contamination, sterility testing, and testing for mycoplasma contamination. The trypsin underwent low pH treatment for virus inactivation and removal (≥24 hours at a pH of <2 and at a pH of <4, respectively) during its manufacturing process. Further, testing for detection of porcine viruses was performed on [redacted] prepared by using the trypsin, as shown in [redacted]. No porcine viruses were detected.

During the drug substance manufacture process, [redacted] is subjected to in-process control tests consisting of bioburden testing, testing for mycoplasma contamination, *in vitro* adventitious virus testing, and testing for detection of bovine viruses.

2.1.5 Manufacturing process development

The following are the main changes made to the manufacturing process during the development of the drug substance (each manufacturing process is referred to as Process A, B, or C [proposed process]).

Table 3 shows the drug substance manufacturing process employed for the manufacture of the formulation used in each clinical study.

- Process A → Process B: Change to [redacted]
- Process B → Process C (proposed process): Change of [redacted], change to [redacted], and addition of [redacted]

After these manufacturing process changes, the quality attributes of pre- and post-change drug substances were assessed. The quality attributes have been shown to be comparable. Because non-clinical studies used the test substance manufactured with a vector genome sequence and through a manufacturing process different from those used in Processes A to C, it is impossible to assess the comparability of the test substance to Luxturna. However, complementary information such as the results of the batch analysis and pharmacological data currently available shows that the non-clinical data can be used for non-clinical safety assessment, according to the applicant [see Section 5.R.1].

Table 3. Manufacturing process of drug substance used for the manufacture of the formulation for clinical studies

Process A	Studies 101, 102, 301
Process B	Study 301
Process C (proposed process)	Study A11301

2.1.6 Characterization

2.1.6.1 Structure and characteristics

Table 4 shows characterizations performed.

Table 4. Characterization items

Physicochemical properties	Description, pH, osmolality [redacted], extractable volume
Identification	Restriction enzyme cleavage patterns, vector genome sequence
Concentration	Content (number of vector genomes)
Activity/titer	Infectious titer, delivery of *RPE*65 transgene to the target cells and expression of RPE65 protein (confirmation by [redacted], expression level assay by [redacted]), [redacted] activity, [redacted]
Safety	Adventitious virus, mycoplasma, bovine virus, rcAAV, bioburden, bacterial endotoxin, insoluble particulate matters, sterility
Purity	[redacted], [redacted], [redacted], host cell DNA, [redacted], plasmid DNA, [redacted], HCP, [redacted], [redacted], [redacted]

2.1.6.2 Product-related substances/product-related impurities

Results of the characterization in Section 2.1.6.1 confirmed that there is no product-related substance with activity other than the product, i.e., the viral vector containing a single-strand DNA. [redacted], replication-competent AAV (rcAAV), product-related Impurity A, and [redacted] were identified as product-related impurities. All of the product-related impurities have been shown to be adequately removed in the manufacturing process. All product-related impurities except product-related Impurity A are adequately controlled by the specifications for the drug substance.

2.1.6.3 Process-related impurities

Host cell DNA, plasmid DNA, Impurity A, host cell protein (HCP), Impurity B, Impurity C, Impurity D, Impurity E, and foreign insoluble matters were handled as process-related impurities. All process-related impurities are adequately controlled by the specifications for the drug substance.

2.1.7 Control of drug substance

The proposed specifications for the drug substance include description, identification (restriction enzyme cleavage patterns), pH, purity ([redacted], [redacted], [redacted], plasmid DNA, Impurity A, host cell DNA, HCP, Impurity B, Impurity E, Impurity D, and Impurity C), microbial limit, rcAAV, bacterial endotoxin, infectious titer, gene expression product (confirmation of RPE65 protein expression), relative titer of gene expression (RPE65 protein expression level assay), [redacted] activity, and content (quantitative polymerase chain reaction [qPCR]).

2.1.8 Stability of drug substance

Table 5 shows the summary of the main stability studies for the drug substance.

Table 5. Summary of the main stability studies for the drug substance

Study	Number of batches*	Storage condition	Study period	Storage form
Long-term stability	3	≤−65°C	18 months	Polypropylene tube with [redacted] cap
Accelerated stability	1	[redacted]°C	[redacted] months	
	1	[redacted]°C	[redacted] months	
Photostability	1	Overall illuminance of ≥1.2 million lux•h, An integrated near ultraviolet energy of ≥200 W•h/m^2, [redacted]°C		

* The drug substance manufactured by the proposed process was used for studies.

In the long-term stability study, an increase in [redacted] was observed in 1 batch at the [redacted]-month time point and [redacted]. However, the percent increase for [redacted] months after the start of study was [redacted] and [redacted] at and after the [redacted]-month time point. Based on these observations, the applicant considers that [redacted] of the batch [redacted]. No clear changes in the quality attributes were noted in other batches throughout the study period.

The accelerated stability study (at [redacted]°C) showed an increase in [redacted].[1)]

The accelerated stability study (at [redacted]°C) showed a more marked increase in [redacted] than that observed in the above accelerated testing (at [redacted]°C). There were tendencies toward decreases in [redacted] and [redacted].

The photostability study showed that the drug substance was photolabile.

Based on the above findings, the shelf life of 18 months has been proposed for the drug substance when stored at ≤−65°C in polypropylene tubes with [redacted] caps, protected from light.

1) Indicates a decrease in [redacted] due to [redacted].

2.2 Drug product

2.2.1 Description and composition of drug product and formulation

The drug product is an injection containing 0.5 mL of the drug substance at a concentration of 5×10^{12} vg/mL, filled in a 2-mL vial. The drug product contains sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate, sodium chloride, poloxamer 188, and [redacted] water as excipients.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of thawing/mixing of the drug substance, sterile filtration, filling/capping, [redacted], and testing. The process before shipping consists of co-packaging of the drug product and the dedicated diluent and labeling.

The sterile filtration process is defined as the critical step.

The manufacturing process for the drug product has been validated on a commercial production scale.

2.2.3 Manufacturing process development

The main changes made to the manufacturing process during the development of the drug product are as shown below (each manufacturing process is referred to as Process D, E, or F [proposed process]). Table 6 shows the manufacturing process for the formulation used in each clinical study.

- Process D → Process E: Changes to [redacted] and [redacted]
- Process E → Process F (proposed process): Changes to [redacted], [redacted], [redacted], and [redacted]

After these manufacturing process changes, the quality attributes of pre- and post-change formulations were assessed. The quality attributes have been shown to be comparable.

Table 6. Manufacturing process of the formulation used in clinical studies

Process D	Studies 101, 102, 301
Process E	Study 301
Process F (proposed process)	Study A11301

2.2.4 Control of drug product

The proposed specifications for the drug product include description, identification (restriction enzyme cleavage patterns), osmolality, pH, purity ([redacted], [redacted]), bacterial endotoxin, extractable volume, foreign insoluble matters, insoluble particulate matters, sterility, [redacted], infectious titer, gene expression products (confirmation of RPE65 protein expression), relative potency of gene expression (quantitation of RPE65 protein expression level), [redacted] activity, and strength (qPCR).

2.2.5 Stability of drug product

Table 7 shows a summary of the main stability studies for the drug product.

Table 7. Summary of main stability studies for the drug product

Study	Number of batches*1	Storage condition	Study period	Storage form
Long-term stability	3	≤−65°C	36 months*2	Cyclic olefine polymer vial with chlorobutyl rubber cap
Accelerated stability	1	[redacted]°C	[redacted] months	
	1	[redacted]°C	[redacted] months	

*1 The product manufactured by the proposed process using the drug substance manufactured by the proposed process was used for studies.
*2 The stability study is ongoing and will continue for up to [redacted] months. Data are available for 1 batch of the drug product stored for 48 months and 2 batches of the drug product stored for 36 months.

The long-term stability study showed an increase in [redacted] in 1 batch at the [redacted]-month time point and [redacted]. However, the percent increase for [redacted] months after the start of the study was [redacted] and [redacted] at and after the [redacted]-month time point. Based on these observations, the applicant considers that [redacted] of the batch [redacted]. No clear change was observed in other batches throughout the study period.

The accelerated stability study (at [redacted]°C) showed a decrease in [redacted] at the [redacted]-month time point. Moreover, there were tendencies toward decreases in [redacted], [redacted], and [redacted].

The accelerated stability study (at [redacted]°C) showed an increase in [redacted],[1)] decreases in [redacted], [redacted], and [redacted]. There were tendencies toward decreases in [redacted] and [redacted].

Since the photostability study on the drug substance has showed that the drug product is photolabile, no photostability testing was conducted on the drug product.

Based on the above findings, a shelf life of 36 months has been proposed for the drug product filled in a cyclic olefin polymer vial with a chlorobutyl rubber cap when it is stored at ≤−65°C in an aluminum pouch placed in a paper box, protected from light.

2.3 Dedicated diluent

2.3.1 Description and composition of product and formulation development

The dedicated diluent is an aqueous solution with the same formulation[2)] of inactive ingredients as that of the drug product without the active ingredient. It is available as 1.7 mL extractable volume of the diluent in a 2-mL vial. One vial of the drug product is supplied with 2 vials of the dedicated diluent.

2.3.2 Manufacturing process

The manufacturing process of the dedicated diluent consists of [redacted], preparation of the diluent, [redacted], sterile filtration, filling/capping, [redacted], and testing.

[redacted] and the sterile filtration process are defined as the critical steps.

2) [redacted] water is used as the solvent for the preparation of the dedicated diluent.

The manufacturing process for the dedicated diluent has been validated on a commercial production scale.

2.3.3 Manufacturing process development

The following are main changes made to the manufacturing process during the development of the dedicated diluent (each manufacturing process is referred to as Process G or H [proposed process]). The dedicated diluent manufactured by Process G was used in clinical studies.

- Process G → Process H (proposed process): Changes to [redacted], [redacted], and [redacted]

2.3.4 Control of dedicated diluent

The proposed specifications for the dedicated diluent include description, osmolality, pH, bacterial endotoxin, extractable volume, foreign insoluble matters, insoluble particulate matters, sterility, and [redacted].

2.3.5 Stability of dedicated diluent

Table 8 shows the summary of the main stability studies for the dedicated diluent.

Table 8. Summary of main stability studies for the dedicated diluent

Study	Number of batches*1	Storage condition	Study period	Storage form
Long-term stability	3	≤−65°C	24 months*2	Cyclic olefine polymer vial with chlorobutyl rubber cap
Accelerated stability	1	[redacted]°C	[redacted] months	
	1	[redacted]°C	[redacted] months	

*1 The dedicated diluent manufactured by the proposed process was used for studies.
*2 The stability study is ongoing and will continue for up to [redacted] months. Data are available for 2 batches of the diluent stored for 48 months and 1 batch of the diluent stored for 24 months.

No change in the quality attributes was noted throughout the study period at the long-term condition, the accelerated condition at [redacted]°C, or the accelerated condition at [redacted]°C.

Based on the above findings, a shelf life of 36 months has been proposed for the dedicated diluent filled in a cyclic olefin polymer vial with a chlorobutyl rubber cap when it is stored at ≤−65°C.

Data from the long-term study are available for only 2 batches of the dedicated diluent stored for up to 36 months. However, the applicant explains that the shelf-life of 36 months for the dedicated diluent is reasonable, taking account of the above data, and as is the case with the drug product, [redacted], for the following reasons:

- [redacted] is [redacted] the dedicated diluent.
- Although [redacted] differs between [redacted] and the dedicated diluent, [redacted] is unlikely to affect [redacted] of the long-term stability study at ≤−65°C.
- Although [redacted] of [redacted], [redacted], and [redacted] was not conducted in the long-term stability study of [redacted], none of them is likely to show any tendency of increase or decrease when stored at ≤−65°C.

2.4 Quality control strategy

The quality control strategy was designed based on the following investigations:

- Identification of critical quality attributes (CQAs):
  On the basis of the information obtained during the development of Luxturna, related knowledge, and other findings, the following CQAs were identified:
  - CQAs of drug substance or drug product
    Description, pH, osmolality, [redacted], extractable volume, restriction enzyme cleavage patterns, vector genome sequencing, strength, infectious titer, delivery of *RPE65* transgene to the target cells and expression of RPE65 protein, [redacted] activity, [redacted], adventitious virus, mycoplasma, bovine virus, rcAAV, microbial limit, bacterial endotoxin, insoluble particulate matters, sterility, [redacted], [redacted], Impurity E, host cell DNA, Impurity A, plasmid DNA, Impurity B, HCP, Impurity C, Impurity D, and [redacted]
  - CQAs of dedicated diluent
    Description, pH, osmolality, bacterial endotoxin, sterility, insoluble particulate matters, [redacted], and extractable volume
- Process characterization:
  Process parameters were classified according to the risk assessment based on their impacts on CQAs, and characterization of each process was performed accordingly.
- Establishment of control method:
  On the basis of the knowledge on the process including the information obtained from the above process characterization, the combination of process parameter control, in-process controls, and specifications was employed to establish the control strategy for the quality attributes of Luxturna. The characteristics of the product are adequately controlled [see Sections 2.1.6.2 and 2.1.6.3 for product-related substances/product-related impurities and process-related impurities, respectively].

2.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the quality of the drug substance, the drug product, and the dedicated diluent was controlled adequately.

3. Primary Pharmacodynamics or Performance and Outline of the Review Conducted by PMDA

The applicant submitted the results from *in vitro* studies in which the expression of RPE65 protein from Luxturna was evaluated using HEK293 cells, together with the following published literature.

3.1 *In vivo* efficacy study of the vector for dogs administered subretinally to Briard dogs with *RPE65* mutation (*Mol Ther.* 2005;12:1072-82[3])

A vector for dogs (AAV2/2-CBA-cRPE65[4]) was administered subretinally to the right eye of Briard dogs[5] with *RPE65* mutation (*RPE65*$^{-/-}$) at a dose of 3.9×10^{10} vg/eye. At 6 months after the administration, production of syn-11-*cis*-retinal oximes in RPE was investigated by high performance

3) Submitted as reference data.
4) Unlike Luxturna, this vector does not contain the stuffer sequence or Kozak sequence, but carries canine *RPE65* gene in place of human *RPE65* gene.
5) These dogs are unable to express RPE65 protein due to biallelic mutation of canine *RPE65* gene. The animals with such mutation exhibit disease phenotype similar to human IRD due to autosomal recessive inheritance of *RPE65* gene.

liquid chromatography (HPLC) in normal Briard dogs and in *RPE65*$^{-/-}$ Briard dogs with or without vector administration. Presence of syn-11-*cis*-retinal oximes was not detected in *RPE65*$^{-/-}$ Briard dogs without vector administration, whereas syn-11-*cis*-retinal oximes were detected in *RPE65*$^{-/-}$ Briard dogs with vector administration. Presence of syn-11-*cis*-retinal oximes was evaluated at multiple subretinal sites. Results showed that presence of syn-11-*cis*-retinal oximes was detected only in the vicinity of the vector administration site and not in other sites.

3.2 *In vivo* efficacy study of the finished product vector administered subretinally or intravitreally to Briard dogs with *RPE65* mutation (*Mol Ther.* 2008;16:458-65[3])

The finished product vector (AAV2-hRPE65v2)[6] was administered subretinally to the left eye, and intravitreally to the right eye, of a *RPE65*$^{-/-}$ Briard dog[4] 3.5 months of age at a dose of 8.25×10^{10} vg (150 µL).

Animals were evaluated at weekly intervals for the first month following injection for changes in pupillary responses of eyes receiving subretinal or intravitreal injection by the swinging flashlight test.[7] Improvement in pupillary constriction response was observed in eyes receiving subretinal injection within 2 weeks post-injection, but hardly in eyes receiving intravitreal injection. Nystagmus in eyes receiving subretinal or intravitreal injection was investigated 1 month post-injection by a rapid eye movement analyzer. Both eyes showed a decrease in nystagmus amplitude.

In addition, the finished product vector was administered subretinally to both eyes of an *RPE65*$^{-/-}$ Briard dog[4] 3.5 months of age at a dose of 8.25×10^{10} vg (150 µL). One *RPE65*$^{-/-}$ Briard dog[4] without vector administration was used as the negative control for the evaluation by electroretinography (ERG).

ERG was evaluated in normal dogs and in a *RPE65*$^{-/-}$ Briard dog with or without vector administration. No wave generation was observed in the *RPE65*$^{-/-}$ Briard dog without vector administration, whereas wave generation was observed in the *RPE65*$^{-/-}$ Briard dog with vector administration at 5 weeks and at 3 months after the administration. RPE65 protein expression in the RPE of *RPE65*$^{-/-}$ Briard dog with vector administration was evaluated by immunohistochemistry. RPE65 protein was detected in RPE cells at the site of administration.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the efficacy of Luxturna in the treatment of IRD with biallelic *RPE65* mutation:

The *in vivo* studies showed pupillary contraction and reduction of nystagmus in the *RPE65*$^{-/-}$ Briard dog injected with the finished product vector. Additionally, in the studies, wave generation was indicated by ERG, and the expression of RPE65 protein in the RPE layer was noted at the administration site. In the study investigating the vector for dogs administered subretinally to *RPE65*$^{-/-}$ Briard dogs, presence of 11-*cis*-retinal was observed. These findings are considered to support the

6) This has the same genome as that of Luxturna, but its comparability with Luxturna has not been confirmed.

7) Pupillary constrictions of the right and left eyes are compared by exposing one eye to light in a dark room for 2 to 4 seconds while observing for the maximum constriction, immediately followed by exposure of another eye to light for 2 to 4 seconds. Under normal conditions, pupillary reflex occurs, causing pupils of both eyes to constrict to a similar extent.

mechanism by which Luxturna improves pupillary reaction and optical defect by delivering expression of RPE65 protein that catalyzes the conversion of all-*trans*-retinyl ester to 11-*cis*-retinol, followed by the production of 11-*cis*-retinal by other enzymes, thereby promoting the normal visual cycle (*Invest Ophthalmol Vis Sci.* 2014;55:6651-72).

PMDA accepted the applicant's explanation.

4. Non-clinical Biological Disposition and Outline of the Review Conducted by PMDA

4.1 Non-clinical biological disposition

4.1.1 Biodistribution

Vector distribution in organs was evaluated in the study in which the finished product vector was administered subretinally to cynomolgus monkeys in a single dose and in the study in which the primary modified vector (AAV2-RPE65v1)[8)] was administered subretinally or intravitreally to beagle dogs in a single dose (Tables 9 and 10). Although the quality attributes of the finished product vector and the primary modified vector have not been confirmed to be comparable to those of Luxturna, the biodistribution of Luxturna can be evaluated based on the results of the above studies because they contain the same AAV2 capsid protein as that of Luxturna, according to the applicant.

8) Unlike Luxturna, this vector does not contain Kozak sequence at the transcriptional start site. In addition, RPE65 protein is expressed at a low level because of unexpected changes at the branching site within the splice acceptor of CBA intron during the manufacturing process. Comparability of quality attributes of this vector to those of Luxturna has not been demonstrated.

Table 9. Study on biodistribution following single injection of the finished product vector

Test system	Route of administration	Observation period	Dose (vg/eye)	Summary of results	Analytical method	Attached document
Male and female cynomolgus monkeys	Subretinal	3 months	3.0×10^{11} 7.5×10^{11}	Vector distribution at the end of the observation period was investigated for 43 types of tissues including the gonad.* The vector was detected at high concentrations in the intraocular fluids (aqueous humor and vitreous humor) of all eyes. The vector was detected at low concentrations in the optic nerve and the optic chiasm, suggesting the possible exposure of the retinal ganglionic cells to the vector. A dose-dependent distribution of the vector in the spleen and liver was observed in all animals tested, albeit at a low concentration. Additionally, the vector was distributed at very low levels in the stomach, mesenteric lymph nodes, and preauricular lymph nodes in some animals in the high-dose group, and also in the colon, duodenum, and trachea of 1 animal of the high dose group. No vector distribution was detected in the following organs or tissues: Skin, skeletal muscles, sciatic nerve, bone marrow, bladder, pancreas, adrenals, kidney, gallbladder, diaphragm, bones, thymus, heart, lung, thyroid, esophagus, aorta, intercostal muscle, spinal cord (lumbar cord, thoracic cord, cervical cord), brain (brainstem, cerebellum, cerebrum), pituitary gland, salivary gland, and gonad (ovary, uterus, uterine cervix, vagina, and male gonad).	The copy number of the vector was determined by qPCR using a DNA sample extracted from each tissue. The analytical method using the qPCR has not been fully validated. A primer set that specifically detects the 63 bp base sequence constituting the finished product vector was used.	4.2.3.1-3

* The vector levels were unmeasurable because of polymerase chain reaction (PCR) inhibition in the following organs of some of the tested animals: Optic nerve, duodenum, uterine cervix, vagina, lung, trachea, esophagus, aorta, intercostal muscle, cardial part of stomach, pylorus of stomach, and pituitary gland.

Table 10. Study on biodistribution following single injection of the primary modified vector

Test system	Route of administration	Observation period	Dose (vg/eye)	Summary of results	Analytical method	Attached document
Male and female dogs (beagle)	Subretinal or intravitreal	3 weeks	1.5×10^{12}	Vector distribution in the following tissues was investigated at the end of the observation period[*1]: Aqueous humor, vitreous humor, optic nerve, pancreas, bone marrow, spleen, kidney, gonad (testis and ovary), brain, skeletal muscle, and preauricular lymph nodes. The vector was detected at high concentrations in the aqueous humor and vitreous fluid, and at low concentrations in the optic nerve and optic chiasm, of all eyes of animals receiving subretinal or intravitreal injection. The vector was not detected in the pancreas, bone marrow, spleen, kidney, gonad (ovary and testis), brain, skeletal muscles, or preauricular lymph nodes.	The copy number of the vector was determined by qPCR using a DNA sample extracted from each tissue. The analytical method using the qPCR has not been fully validated. A primer set that specifically detects the 63 bp base sequence constituting the primary modified vector was used.	4.2.3.1-1
Male and female dogs (beagle)	Subretinal or intravitreal	3 months	1.5×10^{12}	Vector distribution in the following tissues was investigated at the end of the observation period[*2]: Aqueous humor, vitreous humor, optic nerve, pancreas, liver, lung, bone marrow, spleen, kidney, gonad (testis and ovary), brain, skeletal muscle, and preauricular lymph nodes. The vector was detected at high concentrations in the aqueous humor and vitreous fluid of all treated eyes, and at low concentrations in the optic nerve, optic chiasm, and preauricular lymph nodes, of animals receiving subretinal or intravitreal injection. The vector was not detected in the pancreas, liver, lung, bone marrow, spleen, kidney, brain, skeletal muscles, or gonad (ovary and testis). Compared with the results at 3 weeks post-injection, the vector concentration in the intraocular fluid (aqueous humor and vitreous fluid) tended to decrease, suggesting the elimination of the vector.		4.2.3.1-2

*1 The vector levels in the liver and lung were unmeasurable in all of the tested animals because of PCR inhibition. The vector levels in the bone marrow, kidney, brain, preauricular parotid nodes, and skeletal muscles were unmeasurable in some of the tested animals because of PCR inhibition.

*2 The vector levels in the lung, aqueous humor, and vitreous fluid were unmeasurable in some of the tested animals because of PCR inhibition.

4.1.2 Excretion

No non-clinical study was conducted to evaluate the excretion of Luxturna.

4.R Outline of the review conducted by PMDA

The applicant's explanation about the biological disposition.

The single-dose biodistribution study showed the distribution of the vector at high concentrations in the intraocular fluids (aqueous humor in the anterior chamber and vitreous humor) of all eyes tested. The vector was distributed at low concentrations in the optic nerves and the optic chiasm in the treated

eye, suggesting the exposure of the retinal ganglion cells to the vector. In addition, the vector was distributed at low concentrations in the spleen and the liver. Vector distribution in the gonad was not observed in any of the studies.

The above results suggest that extraocular distribution of the vector is minimal following the subretinal administration of Luxturna. Further, the distribution level has been shown to decrease with increasing time after administration, resulting in vector elimination from the body.

PMDA accepted the applicant's explanation.

5. Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted the following data relating to the non-clinical safety of Luxturna: Single-dose toxicity studies in dogs and monkeys receiving the finished product vector, repeated-dose toxicity studies in dogs and monkeys receiving the finished product vector, and a single-dose toxicity study in dogs receiving the primary modified vector.

5.1 Single dose toxicity

Single-dose toxicity studies were conducted using the finished product vector and the primary modified vector (Tables 11 and 12). Changes observed in both studies included detachment of retina and RPE, and scar formation, which were attributed to traumatic changes caused by the injection procedures.

In the single-dose toxicity study using the primary modified vector, infiltration of inflammatory cells in the brainstem, midbrain, and choroid plexus were observed at 3 weeks post-injection, suggesting immune responses to the vector, but there was no evidence of vector presence in the brain at this time point [see Section 4.1.1]. No similar findings were noted at 3 months post-injection or in the single-dose toxicity study using the finished product vector which expresses RPE65 protein at a higher level. Because the above changes were mild, transient, and reversible, the infiltration of inflammatory cells in the brain was considered to be of low toxicological significance.

Table 11. Single-dose toxicity study of finished product vector

Test system	Route of administration	Observation period	Dose (vg/eye)	Main findings for Luxturna	Attached document
Male and female cynomolgus monkeys	Subretinal (1 or 2 eyes[*1])	3 months	0 (vehicle) 3.0×10^{11} 7.5×10^{11}[*2]	Hypertrophy/aggregation/cell detachment of RPE, loss of visual cells, and pigmentation of macrophages	4.2.3.1-3
Male and female dogs (*RPE65*$^{-/-}$ Briard dogs[*3])	Subretinal	5 weeks to 3 months	8.25×10^{10}	(At 5 weeks and 3 months) Abnormalities associated with missing RPE65 protein (vacuolization/pigmentation/atrophy/hypertrophy of RPE, subretinal gliosis, atrophy of external granular layer) (At 3 months) RPE cell detachment, scarring around the injection site	4.2.3.1-4 (reference)

*1 In the single eye administration group, vehicle was injected to the eye not treated with the finished product vector.
*2 Corresponds to 5 times the clinical dose (1.5×10^{11} vg/eye).
*3 The animals cannot express RPE65 protein due to biallelic mutation of canine *RPE65* gene. The phenotype is similar to that of human IRD caused by autosomal recessive inheritance of *RPE65* gene.

Table 12. Single-dose toxicity study of the primary modified vector

Test system	Route of administration	Observation period	Dose (vg/eye)	Main findings for Luxturna	Attached document
Male and female dogs (beagle)	Subretinal or intravitreal	3 weeks	0 (vehicle) 1.5×10^{12}	Inflammatory cell infiltration around the blood vessels of the inner layer of the retina and in the posterior chamber of eye, flattening/desquamation of RPE in the central retina, hyperplasia of RPE cells Inflammatory cell infiltration around the blood vessels in the brain stem, midbrain, and choroid plexus	4.2.3.1-1
Male and female dogs (beagle)	Subretinal or intravitreal	3 months	0 (vehicle) 1.5×10^{12}	Inflammatory cell infiltration around the blood vessels in the retina and choroid, retinal degeneration, loss of RPE cell layer at the site of inflammation, loss of outer nuclear and inner nuclear layers, pseudorosette formation of outer nuclear layer accompanying the adhesion of Bruch's membrane	4.2.3.1-2

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted using the finished product vector (Table 13). All studies showed scar formation/rosette formation in the retina (retinal detachment associated with abnormal RPE cell arrangement), which were considered to be traumatic changes caused by the injection procedures. In addition, inflammatory findings were observed within the vitreous body, subretinal space, and optic papilla. They were not observed after the single injection [see Section 5.1], suggesting that these observations are unlikely to pose safety concerns because Luxturna is administered in a single dose in clinical settings.

Table 13. Repeated-dose toxicity studies

Test system	Route and method of administration	Observation period	Dose (vg/eye)	Main findings	Attached document
Male and female dogs (unknown breeds)	Subretinal: Injection in the left eye, followed by injection in the right eye after 3 months, then by re-injection in the right eye after approximately 1 month	6.5 months	1.5×10^{11}	Scar and rosette formation around the injection site, thinning of visual cell layer, inflammation in vitreous body/subretinal space/optic nerve head	4.2.3.2-1 (reference)
Male and female dogs (*RPE65*$^{-/-}$ Briard dogs*1)	Subretinal: Injection in the right eye, followed by injection in the left eye after 2 weeks	2 years	1.5×10^{11}	Scar and rosette formation around the injection site, RPE hypertrophy, inflammation	4.2.3.2-2 (reference)
Male and female dogs (*RPE65*$^{-/-}$ Briard dogs*1)	Subretinal or subchoroidal: Subretinal injection in both eyes, followed by subretinal injection in the left eye after 1 month Or subchoroidal injection in the left eye and subretinal injection in the right eye, followed by subretinal injection in the left eye after 1 month Or subretinal injection in the right eye, followed by subretinal injection in the left eye after 1 month.	2.5-6 months	8.25×10^{10} 1.1×10^{11} 1.5×10^{11}	Rosette formation, choroidal inflammation, cell infiltration	4.2.3.2-3 (reference)
Female cynomolgus monkeys and rhesus monkeys*2	Subretinal: Injection in the right eye, followed by injection in the left eye after 2 months	6-7 months	1.5×10^{11}	Scar around the injection site, inflammation in retina/optic nerve/subretinal space/vitreous body*3	4.2.3.2-4 (reference)

*1 The animals cannot express RPE65 protein due to biallelic mutation of canine *RPE65* gene. The phenotype is similar to that of human IRD caused by autosomal recessive inheritance of *RPE65* gene.
*2 The animals were anti-AAV2 antibody-positive due to the prior exposure to AAV vector other than Luxturna.
*3 Not correlated with the anti-AAV2 antibody titer.

5.3 Other safety evaluations

5.3.1 Possibility of chromosomal integration of transgene

The applicant's explanation:

The transgene of Luxturna is unlikely to be integrated into chromosomes, for the following reasons:

- Wild-type AAV is integrated into human chromosome 19 selectively, whereas *rep* gene encoding Rep protein involved in the chromosomal integration has been deleted from Luxturna, suggesting that chromosomal integration does not occur.
- Luxturna is administered subretinally to the retinal tissue as the target. The retinal tissue has very limited mitotic capacity, with few cells in stage capable of DNA replication or repair that may induce chromosomal integration.

5.3.2 Possibility of tumorigenicity and carcinogenicity

The applicant's explanation:

Luxturna is unlikely to induce tumorigenicity or carcinogenicity, based on the following observations:

- Following the subretinal administration of Luxturna, extraocular distribution of the vector was minimal [see Section 4.R], and there were no findings suggestive of tumorigenicity in the general toxicity studies of Luxturna [see Sections 5.1 and 5.2].

- The risk of gene integration of Luxturna is probably minimal [see Section 5.3.1].

5.3.3 Reproductive and developmental toxicity

The applicant's explanation:

The subretinal administration of Luxturna poses only minimal reproductive and developmental risk, in view of the following observations:

- Subretinal administration of the finished product vector or the primary modified vector to dogs or monkeys did not cause histopathological changes or vector distribution in reproductive tissues.
- The risk of gene integration of Luxturna is probably minimal [see Section 5.3.1].

5.3.4 Safety in administration to children

The applicant's explanation:

Administration of Luxturna to children does not cause any safety problem, in view of the following observations:

- In the single-dose toxicity study using the finished product vector [see Section 5.1], administration of the finished product vector to *RPE65*$^{-/-}$ Briard dogs 3.5 months of age did not pose any safety concerns. This age corresponds to 3 to 4 years of age in humans (*Contemp Top Lab Anim Sci.* 2002;41:21-6).
- In a study in which AAV2/1 vector, a vector different from that of Luxturna, was delivered subretinally to intrauterine fetuses and neonates of *RPE65*$^{-/-}$ mice for transduction of the human *RPE65* gene, no morphological abnormalities were observed in the eyeballs or retina (*Mol Ther.* 2004:9;182-8).

5.3.5 Safety evaluation of process-related impurities

The applicant's explanation:

In view of the results of the single subretinal dose toxicity study [Section 4.2.3.1-3] in which cynomolgus monkeys were treated with the finished product containing impurities to a similar extent to those of Luxturna, the process-related impurities of Luxturna are unlikely to pose safety concerns in clinical use.

5.3.6 Safety evaluation of excipients

The applicant's explanation about the excipients contained in Luxturna, i.e., buffer (sodium dihydrogenphosphate monohydrate, disodium hydrogen phosphate dihydrate), sodium chloride, poloxamer 188, sterilized purified water, sodium hydroxide, and hydrochloric acid:

The excipients do not pose any safety concerns in the clinical use of Luxturna, in view of the results of the general toxicity study on Luxturna and of the previous use of these compounds as drug excipients in Japan.

5.R Outline of the review conducted by PMDA

From the submitted data and the following review, PMDA concluded that there were no particular concerns about the non-clinical safety of Luxturna.

5.R.1 Appropriateness of using the finished product vector and the primary modified vector as test articles for toxicity studies

PMDA asked the applicant to explain the appropriateness of the safety evaluation of Luxturna based on the results of the single-dose toxicity study using the finished product vector or the primary modified vector neither of which is confirmed to be comparable to Luxturna in quality attributes [See Section 5.1] and on the results of the repeated-dose toxicity study using the finished product vector [See Section 5.2].

The applicant's response:

The results of the single-dose and the repeated-dose toxicity studies using these vectors are extrapolatable to the safety evaluation of Luxturna, for the following reasons:

- Because both the finished product vector and the primary modified vector contain the same AAV2 capsid protein as Luxturna, toxicity associated with the capsid protein is evaluable with the data from the above studies.
- In the non-clinical study in *RPE65*$^{-/-}$ Briard dogs, the administration of the finished product vector resulted in the expression of RPE65 protein and improvement in visual function [see Section 3.2]. The toxicity of RPE65 protein is also evaluable with the data from this study.

PMDA accepted the applicant's explanation.

6. Clinical Biological Disposition and Outline of the Review Conducted by PMDA

The clinical biological disposition of Luxturna was investigated based on the information obtained from Studies 101, 102, 301, and A11301.

6.1 Clinical pharmacology

Changes over time in the concentration of Luxturna genomic DNA (gDNA) after administration of Luxturna were determined by qPCR in Studies 101, 102, 301, and A11301. Table 14 shows test samples, dosage regimen, sampling time, and the limit of quantification (LOQ) of qPCR.

Table 14. Samples, dosage regimen, sampling time, and LOQ of qPCR in each study

Study identifier	Test samples	Dosage regimen	Sampling time	LOQ of qPCR
101	Tear, serum, and PBMC	Low dose: 1.5×10^{10} vg/150 µL (n = 3) Medium dose: 4.8×10^{10} vg/150 µL (n = 6[*1]) High dose: 1.5×10^{11} vg/300 µL (n = 3) Single subretinal injection in one eye	Day 0, 1, 2, 3	Approx. 10 copies/µg DNA[*2] The level at least LOD and below LOQ was defined as PNQ.
102	Tear, serum, and PBMC	1.5×10^{11} vg/300 µL (n = 11) Single subretinal injection (in the contralateral eye of subjects treated in Study 101)[*3]	Day 1, 2, 3, 7	
301	Tear, blood, and serum	1.5×10^{11} vg/300 µL (n = 29) Sequential subretinal injections in each eye[*4]	Day 0A/B, 1A/B, 3A/B, 14B, 30B, 90B, 180B (tear samples only), Year 1B[*5]	10 copies/µg DNA
A11301	Tear, blood, and serum	1.5×10^{11} vg/300 µL (n = 4) Sequential subretinal injections in each eye[*4]	Day 0A/B, 1A/B, 3A/B, 14B, 30B, 90B, 180B (tear samples only), 270B (tear samples only), Year 1B[*5]	50 copies/µg DNA

*1 One subject who showed foveal dehiscence at the time of injection received re-injection. The estimated total subretinal dose was 3.2×10^{10} vg/100 µL.
*2 The qPCR method used in Studies 101 and 102 was not fully validated.
*3 The interval between the first- and second-eye injections was ≥1 year.
*4 The interval between the first- and second-eye injections ranged from 6 to 18 days.
*5 "A" indicates the number of days after the first-eye injection, and "B" indicates the number of days after the second-eye injection.

The following sections address changes over time in the concentrations of Luxturna gDNA in tears, blood, serum, and peripheral blood mononuclear cells (PBMC) after the administration of Luxturna in Studies 101, 102, 301, and A11301. It should be noted that the data allow only qualitative evaluation because the copy number of Luxturna DNA contained in 1 mL of blood or in 1 swab of tears is unknown (the test procedure did not require recording of the sample volume before DNA extraction).

6.1.1 Study 101

In 1 of 3 subjects in the low-dose cohort, tear samples from the injected eye were positive on Day 1, but Luxturna gDNA levels in the samples were below the limit of detection (LOD) on Day 2. Luxturna gDNA levels in other samples of this subject and all samples of other subjects were below the LOD at all time points evaluated.

In 2 of 6 subjects in the medium-dose cohort, tear samples from the injected eye were positive on Day 1, but Luxturna gDNA levels in the samples were below the LOD on Day 2. In another subject, Luxturna gDNA levels in tear samples from the injected eye were below the LOD on Day 1 but were detected in the samples on Day 2, then again fell below the LOD on Day 6. Luxturna gDNA levels in other samples of these subjects and all samples of other subjects were below the LOD at all time points evaluated.

In 2 of 3 subjects in the high-dose cohort, tear samples from the injected eye were positive on Day 1, but Luxturna gDNA levels in the samples were below the LOD on Day 3 in one subject, and at Week 2 in the other subject. In the latter subject, the tear samples from the uninjected eye as well as serum and PBMC samples were positive on Day 1, but Luxturna gDNA levels in the samples fell below the LOD at Week 2, as was the case with the injected eye. In the remaining 1 subject in the high-dose cohort, PBMC samples became positive on Day 3, but Luxturna gDNA levels in the samples fell

below the LOD at Week 2. Luxturna gDNA levels in other samples of this subject and all samples of other subjects were below the LOD at all time points evaluated.

6.1.2 Study 102

Tear samples from the injected eye were positive on Day 1 in 7 of 11 subjects. However, Luxturna gDNA levels fell below the LOD by Day 3 in 4 of the 7 subjects and at Week 2 in the remaining 3 subjects. In 5 of 11 subjects, serum or PBMC samples were positive on Day 1 or 2. Among the 5 subjects, Luxturna gDNA levels fell below the LOD by Day 3 in 3 subjects, and at Week 1 in 1 subject. In the remaining 1 subject, Luxturna gDNA levels in serum and PBMC samples were below the LOD until Day 3, but Luxturna gDNA was detected in serum samples at Week 2 and then fell below the LOD at Week 4. Luxturna gDNA levels in other samples of the subjects and all samples of other subjects were below the LOD at all time points evaluated.

6.1.3 Study 301

Tear samples from the injected eye were positive at the time point of Day 1A or Day 1B in 13 of 29 subjects, but Luxturna gDNA levels fell below the LOQ within 3 days post-injection in 8 of the 13 subjects, at 14 days post-injection in 3 subjects, and at 10 and 30 days post-injection in each of the remaining 2 subjects. In all other subjects, Luxturna gDNA levels in tear samples were below the LOQ at all time points evaluated.

Serum samples were positive at some time points of Day 1A to 3A or Day 1B to 3B in 3 of 29 subjects, but Luxturna gDNA levels were below the LOQ at the time point of Day 14B. Luxturna gDNA levels in serum samples in the remaining 26 subjects were below the LOQ at all time points evaluated. Luxturna gDNA levels in the blood samples from all subjects were below the LOQ at all time points evaluated.

6.1.4 Study A11301

Luxturna gDNA levels in all samples from all subjects were below the LOQ at all time points.

6.2 Immune responses to administration to Luxturna

Anti-AAV2 antibody titer,[9)] anti-RPE65 antibody titer,[10)] and T cell response to AAV2 capsid protein and RPE65 protein[11)] were evaluated for a maximum of 3 years after administration of Luxturna in Studies 101 and 102 and for 1 year after the second-eye injection in Studies 301 and A11301. The immune reactions were mild at all doses evaluated and throughout the evaluation period.

6.R Outline of the review conducted by PMDA

The applicant's explanation about the clinical biological disposition of Luxturna:

Vector secretion or distribution in tears or blood was transient or scarcely detectable in all of the studies. Luxturna gDNA was detected to a certain extent in tear samples from the injected eye up to 14

9) In Studies 101 and 102, anti-AAV2, neutralizing titer against Luxturna activity in serum and plasma was evaluated using HEK293 cells. In Studies 301 and A11301, anti-AAV2 antibody was evaluated by enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence immunoassay (ECLIA), respectively.

10) In Studies 101 and 102, anti-RPE65 antibody titer was evaluated by ELISA.

11) In Studies 101, 102, 301, and A11301 studies, T cell responses were evaluated by interferon-gamma enzyme-linked immunosorbent spot (IFN-γ ELISPOT).

days post-injection, but Luxturna gDNA levels in serum and PBMC samples were extremely low, suggesting that Luxturna gDNA is unlikely to be excreted in urine or feces. Differences in the biological disposition of Luxturna between Japanese and non-Japanese subjects were investigated. Luxturna gDNA levels in all samples were below the LOQ at all time points evaluated in all subjects of Study A11301 involving Japanese patients and, in Studies 101, 102, and 301, Luxturna gDNA levels in samples from non-Japanese subjects were also low. These findings suggest that there is no significant difference in the tendency of the biological disposition or excretion of Luxturna between Japanese and non-Japanese subjects.

Immune reactions to the administration of Luxturna were mild at all doses and at all evaluation time points investigated. Anti-AAV2 antibody titer showed a small and transient increase from baseline in some subjects, but no adverse events related to host immune response were observed.[12)] There were no subjects who showed clinically significant cytotoxic T-cell response to either AAV2 capsid protein or to RPE65 protein. There were no significant differences in the above immune reactions between Japanese and non-Japanese subjects.

PMDA accepted the applicant's explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results from 4 clinical studies listed in Table 15 as efficacy and safety evaluation data.

Table 15. List of clinical studies evaluating efficacy and safety

Data category	Region	Study identifier	Phase	Study population	No. of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Foreign	101	I	Patients with biallelic *RPE65* mutation-associated IRD	12	A single subretinal injection of Luxturna into one eye at a dose of 1.5×10^{10} vg/150 µL, 4.8×10^{10} vg/150 µL, or 1.5×10^{11} vg/300 µL	Safety Efficacy
	Foreign	102	I	Patients who completed 1-year follow-up period in Study 101	11	A single subretinal injection of Luxturna into one eye (in the contralateral eye of the subjects treated in Study 101) at a dose of 1.5×10^{11} vg/300 µL	Safety Efficacy
	Foreign	301	III	Patients with biallelic *RPE65* mutation-associated IRD	31	Sequential subretinal injections of Luxturna into each eye at a dose of 1.5×10^{11} vg/300 µL each	Efficacy Safety
	Japan	A11301	III	Patients with biallelic *RPE65* mutation-associated IRD	4	Sequential subretinal injections of Luxturna into each eye at a dose of 1.5×10^{11} vg/300 µL each	Efficacy Safety

[12)] There were no reports of adverse events coded to "Antibody test abnormal," "Antibody test positive," "Drug specific antibody present," "DNA antibody positive," or "Antibody-dependent enhancement positive during treatment" in MedDRA PT version 24.0.

7.1 Evaluation data

7.1.1 Foreign clinical studies

7.1.1.1 Foreign phase I study (CTD 5.3.5.2-2, Study 101 [September 2007 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at a single study site in each of the US and Italy to investigate the safety and efficacy of Luxturna in non-Japanese patients aged ≥8 years with biallelic *RPE65* mutation-associated IRD (target sample size, 12 subjects [3 in low-dose cohort, 6 in medium-dose cohort, 3 in high-dose cohort]).

Table 16 shows main inclusion and exclusion criteria.

Table 16. Main inclusion/exclusion criteria

Inclusion criteria	Patients who meet all of the following criteria: • Diagnosis of LCA due to biallelic *RPE65* mutation based on the confirmation of molecular/genetic diagnosis by a CLIA-certified laboratory • ≥8 years of age at time of subretinal administration • Visual acuity ≤20/160 or visual field <20 degrees for the eye to be injected
Exclusion criteria	• Patients who have insufficient viable retinal cells and who meet any of 1) to 3) below: 1) <1 disc area of retina that is not involved in complete retinal degeneration (geographic atrophy, retinal thinning with a tapetal sheen reflex, or confluent intraretinal pigment migration), as determined by ophthalmoscopy 2) Areas of retina with <100 μm thickness shown on OCT 3) Areas of retina with absence of neural retina • Patients with prior intraocular surgery within 6 months before screening • Patients with pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study results • Patients with neutralizing antibodies against AAV2 >1:1,000 by immunological test

The study consisted of a baseline period (maximum 4 weeks), a treatment period (day of Luxturna administration), a follow-up period (1 year after Luxturna administration), and a long-term follow-up period[13)] (1-5 years after Luxturna administration). The study included the low-dose cohort, the medium-dose cohort, and the high-dose cohort. Subjects were allocated to the low-dose cohort first, followed by sequential allocation to the medium cohort and then to the high-dose cohort, based on the safety and efficacy assessment by the independent data safety monitoring committee. The safety evaluation was conducted according to the World Health Organization (WHO) toxicity scale to which was added evaluation of ocular adverse events.

As a general rule, a single dose of Luxturna was administered by subretinal injection to one eye with lower visual acuity after vitrectomy at 1.5×10^{10} vg/150 μL in the low-dose cohort, at 4.8×10^{10} vg/150 μL in the medium-dose cohort, and at 1.5×10^{11} vg/300 μL in the high-dose cohort. In order to minimize the inflammation associated with the Luxturna injection procedures and to reduce immune reactions to capsid protein and RPE65 protein, oral systemic corticosteroid (prednisone) was administered. Prednisone was administered at 1 mg/kg/day (maximum of 40 mg/day) for 10 days, starting 3 days before subretinal injection of Luxturna, followed by the dose at 0.5 mg/kg/day (maximum of 20 mg/day) for 7 days, and discontinued 14 days after Luxturna administration.

Luxturna was administered to the test eye of all of the 12 subjects enrolled in the study (3 in low-dose cohort, 6 in medium-dose cohort, and 3 in high-dose cohort), and all of them were included in the

13) Data from subjects who completed the evaluation at 1 year after administration in Study 101 were handled as those of Study 101 until their participation in Study 102 (the extension study) or the data cut-off date of [redacted], 20[redacted].

efficacy and safety analysis populations. Among them, 11 subjects had completed the study at the data cut-off date and entered Study 102. The remaining 1 subject was found to have glaucoma in the uninjected eye after Luxturna administration. This subject was considered ineligible for enrollment in Study 102, and therefore entered the long-term follow-up period.

Neither primary nor secondary endpoints were used to evaluate the efficacy. Instead, efficacy was evaluated based on other endpoints, such as visual acuity[14)] and full-field light sensitivity threshold (FST).[15)]

Visual acuity was assessed, and 58.3% (7 of 12) of subjects showed clinically significant improvement from baseline (a decrease by ≥0.3 logMAR [logarithmic minimum angle of resolution] from baseline [improvement by ≥15 letters or ≥3 lines]) at 1 year after Luxturna administration. Table 17 shows changes from baseline in visual acuity at 1 year after Luxturna administration in 12 subjects ([redacted], [redacted], [redacted] in the low-dose cohort; [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] in the medium-dose cohort; [redacted], [redacted], [redacted] in the high-dose cohort).

Table 17. Change from baseline in visual acuity (Luxturna-injected eye; Holladay scale; unit, logMAR) at 1 year after Luxturna administration (Study 101, efficacy analysis population)

Cohort	Patient No.	Baseline	Change from baseline at 1 year after administration
Low dose	[redacted]	2.75	−1.32
	[redacted]	2.75	−1.24
	[redacted]	1.39	−0.35
Medium dose	[redacted]	1.06	−0.46
	[redacted]	1.34	0.48
	[redacted]	1.32	0.3
	[redacted]	1.03	0.01
	[redacted]	1.47	−0.22
	[redacted]	1.01	−0.5
High dose	[redacted]	3.50	−1
	[redacted]	1.86	−0.25
	[redacted]	0.96	−0.53

As for FST, light sensitivity was assessed in 8 subjects with evaluable data before and after administration[16)] ([redacted], [redacted], [redacted], [redacted], [redacted] in medium-dose cohort; [redacted], [redacted], [redacted] in high-dose cohort), using FST (white light; unit, dB) as the index. In all subjects, FST decreased (light sensitivity increased) in the injected eye, with a marked increase in light sensitivity in the injected eye compared to the contralateral (uninjected) eye. Table 18 shows the change from baseline in FST in the injected eye of 7 subjects[17)] evaluated for FST at 1 year after Luxturna administration.

[14)] An ETDRS vision chart was used. In subjects unable to recognize the largest letter on the ETDRS vision chart, "off-chart" visual acuity was measured and the measurements were converted to the logMAR scores using Holladay and Lange scales for evaluation.

[15)] The test whereby the light sensitivity of the entire retina and its threshold were evaluated by the measurement of the subject's perception of different brightness levels, thereby to subjectively measure photosensitivity related to visual function. The subject, after dark adaptation in a dark room, answered whether he/she noticed light pulses repeated at various brightness, based on which the threshold of recognizable brightness was calculated. The threshold was evaluated based on the relative scale (dB) in Studies 101 and 102, and on the absolute luminosity scale (cd.s/m^2) in Studies 301 and A11301.

[16)] Data could not be collected from 3 subjects in the low-dose cohort and from 1 subject in the medium-dose cohort because FST became measurable only after the start of the study in these subjects.

[17)] FST at 1 year after Luxturna administration could not be evaluated in 1 subject ([redacted]) in the high-dose cohort.

Table 18. Change from baseline in FST (Luxturna-injected eye; white light; unit, dB) at 1 year after Luxturna administration (Study 101, efficacy analysis population)

Cohort	Patient No.	Baseline	Change from baseline at 1 year after administration
Medium dose	[redacted]	3.6	−8.1
	[redacted]	7.4	−18.5
	[redacted]	−0.8	−22.7
	[redacted]	5.9	−9.4
	[redacted]	5.0	−22.4
High dose	[redacted]	12.0	−8.4
	[redacted]	12.3	−33.7
	[redacted]	5.6	-*

* Change from baseline in FST at 2 and 3 years after Luxturna administration was –8.9 and –13.9, respectively

Adverse events were observed in all subjects within 1 year after Luxturna administration. A causal relationship to Luxturna was ruled out for all adverse events. Table 19 shows adverse events occurring in ≥2 subjects in the entire population.

Table 19. Adverse events observed in ≥2 subjects in the entire population (Study 101, safety analysis population)

	Low-dose cohort (N = 3)	Medium-dose cohort (N = 6)	High-dose cohort (N = 3)	All subjects (N = 12)
Subjects with any adverse event	3 (100)	6 (100)	3 (100)	12 (100)
Conjunctival hyperaemia	3 (100)	4 (66.7)	1 (33.3)	8 (66.7)
Pyrexia	2 (66.7)	4 (66.7)	1 (33.3)	7 (58.3)
Leukocytosis	2 (66.7)	3 (50.0)	1 (33.3)	6 (50.0)
Abdominal discomfort	1 (33.3)	3 (50.0)	1 (33.3)	5 (41.7)
Headache	0	4 (66.7)	1 (33.3)	5 (41.7)
Influenza	0	2 (33.3)	2 (66.7)	4 (33.3)
Nasopharyngitis	0	2 (33.3)	2 (66.7)	4 (33.3)
Blood creatinine increased	0	3 (50.0)	1 (33.3)	4 (33.3)
Hypoglycaemia	2 (66.7)	1 (16.7)	1 (33.3)	4 (33.3)
Haematuria	1 (33.3)	2 (33.3)	1 (33.3)	4 (33.3)
Cough	1 (33.3)	2 (33.3)	1 (33.3)	4 (33.3)
Ear infection	1 (33.3)	1 (16.7)	1 (33.3)	3 (25.0)
Contusion	0	2 (33.3)	1 (33.3)	3 (25.0)
Hyperglycaemia	1 (33.3)	2 (33.3)	0	3 (25.0)
Tracheitis	2 (66.7)	0	0	2 (16.7)
Corneal abrasion	0	1 (16.7)	1 (33.3)	2 (16.7)
Fall	0	1 (16.7)	1 (33.3)	2 (16.7)
Neck pain	1 (33.3)	1 (16.7)	0	2 (16.7)
Proteinuria	1 (33.3)	1 (16.7)	0	2 (16.7)
Acne	1 (33.3)	1 (16.7)	0	2 (16.7)

Medical Dictionary for Regulatory Activities (MedDRA) ver.14.0
n (%)

No death occurred. A serious adverse event (anal fistula) was observed in 1 subject of the low-dose cohort. Its causal relationship to Luxturna or injection procedures was ruled out, and the adverse event resolved without sequelae.

7.1.1.2 Foreign phase I study (CTD 5.3.5.2-3, Study 102 [ongoing since November 2010 (data cut-off [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted at a single study site in the US to investigate the safety and efficacy of Luxturna in patients who had completed Study 101.

Table 20 shows the main inclusion/exclusion criteria.

Table 20. Main inclusion/exclusion criteria

Inclusion criteria	Patients who met all of the following criteria: • Patients who received Luxturna in one eye in Study 101. • Visual acuity equal to or greater than light perception • Sufficient viable retinal cells in the contralateral, previously uninjected eye. Must have one of the following: 1) An area of retina within the posterior pole of >100 μm thickness. 2) ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole 3) A remaining visual field within 50 degrees of fixation
Exclusion criteria	• Patients with prior intraocular surgery within 6 months before screening • Patients with pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study endpoints • Patients who used retinoid compounds or precursors, which might potentially interact with the biochemical activity of RPE65 protein, within 18 months before screening

The study consisted of a baseline period (maximum of 8 weeks), a treatment period (day of Luxturna administration), and a follow-up period (primary period, up to 1 year after Luxturna administration; long-term follow-up,[18)] 14 years after Luxturna administration).

A single dose of Luxturna was administered by subretinal injection at 1.5×10^{11} vg/300 μL to the contralateral eye of the subjects treated in Study 101, after vitrectomy. In order to minimize inflammation associated with injection procedures and to reduce immune reactions to capsid protein and RPE65 protein contained in Luxturna, oral systemic corticosteroid (prednisone) was administered according to the same dosage regimen as that employed in Study 101.

Of 12 subjects who completed Study 101, 11 subjects entered Study 102, received the injection of Luxturna, and were included in the efficacy and safety analysis populations. The remaining 1 subject was ineligible for enrollment in Study 102 because of glaucoma found in the eye to be injected. None of the subjects discontinued the study after Luxturna administration. All of them completed the evaluation at 1 year after Luxturna administration, and were still on long-term follow-up at the data cut-off time point.

Table 21 shows the change from baseline in FST (white light; unit, dB) of the injected eye at 1 year after Luxturna administration in Study 102. FST decreased in 8 of 11 subjects.[19)] In 7 of the 8 subjects, FST decreased by >10 dB defined as the clinically significant threshold.

[18)] Subjects entered the long-term follow-up study (Study LTFU-01) within 1 to 6 years after Luxturna administration in Study 102, and were to be followed up for a total of 15 years after Luxturna administration in Study 102.
[19)] FST was considered unchanged in [redacted].

Table 21. Change from baseline in FST (eye injected with Luxturna in Study 102; white light; unit, dB) at 1 year after Luxturna administration (Study 102, efficacy analysis population)

Subject ID	Baseline	Change from baseline at 1 year after administration
[redacted]	9.0	−36.0
[redacted]	8.3	−45.6
[redacted]	6.6	−8.2
[redacted]	−20.1	2.9
[redacted]	6.8	1.7
[redacted]	4.3	−18.1
[redacted]	−10.4	−17.9
[redacted]	5.6	−25.2
[redacted]	−3.6	−13.7
[redacted]	8.0	−0.2
[redacted]	1.0	−38.1

The multi-luminance mobility test (MLMT)[20)] score of the injected eye in Study 102 was considered evaluable in 8 of 11 subjects (2 of 3 subjects in part 1 evaluated according to the old procedure and 6 of 8 subjects in part 2 evaluated according to the new procedure). In all 8 subjects, the MLMT score increased at 1 year after Luxturna administration from baseline (Table 22).

Table 22. Change from baseline in MLMT score (the injected eye in Study 102) at 1 year after Luxturna administration (Study 102, efficacy analysis population)

Subject ID	Baseline	Change from baseline at 1 year after administration
[redacted]*1	0	+6
[redacted]	3	+3
[redacted]	2	+1
[redacted]*2	-	-
[redacted]*3	-	-
[redacted]	3	+2
[redacted]	4	+2
[redacted]	3	+3
[redacted]*1	0	+3
[redacted]*1*4	-	-
[redacted]	5	+1

*1 Evaluated according to the old procedure at baseline, and according to the new procedure at 1 year after administration.
*2 The subject was able to navigate the MLMT course without problems under the minimum light level of 1 Lux at baseline. This precluded the assessment of improvement in the MLMT score after Luxturna administration.
*3 The behavior of the subject was atypical, supposedly due to the effect of *RDH-12* gene abnormality and/or deposit at the optic nerve disc the subject had at baseline of Study 101. This precluded the assessment.
*4 The subject failed to pass the MLMT course under the maximum light level (based on the old procedure) at baseline. This precluded the assessment.

In Study 102, adverse events were reported in all subjects within 1 year after Luxturna administration. A causal relationship to Luxturna was ruled out for all adverse events. Table 23 shows adverse events reported in ≥2 subjects.

[20)] A test for evaluating the mobility under various light levels [see Section 7.1.1.3]. The initially developed MLMT was evaluated in an exploratory manner in Study 101, and some of the procedures (addition of light levels, scoring method, etc.) were changed during the periods of Studies 101 and 102 ([redacted] 20[redacted]). Subsequently, the MLMT was standardized based on the results of Studies 101 and 102 and on the results of the discussion with the US FDA before its use in Study 301 [see Section 7.1.1.3]. The MLMT scores obtained in Studies 101 and 102 should therefore be regarded as exploratory data. In the revised procedures, subjects underwent a test with the bandage on the eye injected in Study 101.

Table 23. Adverse events reported in ≥2 subjects in the entire population (Study 102, safety analysis population)

	All subjects (N = 11)
Subjects with any adverse event	11 (100)
Pyrexia	4 (36.4)
Influenza	4 (36.4)
Blood creatinine increased	4 (36.4)
Headache	4 (36.4)
Haematuria	4 (36.4)
Proteinuria	4 (36.4)
Cataract	3 (27.3)
Dellen	3 (27.3)
Abdominal discomfort	3 (27.3)
Nausea	3 (27.3)
Vomiting	3 (27.3)
Oropharyngeal pain	3 (27.3)
Abdominal pain	2 (18.2)
Diarrhoea	2 (18.2)
Gastrooesophageal reflux disease	2 (18.2)
Seasonal allergy	2 (18.2)
Nasopharyngitis	2 (18.2)
Sinusitis	2 (18.2)
Contusion	2 (18.2)
Excoriation	2 (18.2)
Intraocular pressure increased	2 (18.2)
Hyperglycaemia	2 (18.2)
Hypoglycaemia	2 (18.2)
Cough	2 (18.2)

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n (%)

No death occurred. A serious adverse event (intraocular pressure increased) was reported in 1 subject. This subject had to be hospitalized for monitoring after laser iridectomy and for ensuring adherence to taking an ocular hypotensive drug. The adverse event was considered serious. The adverse event was poorly controlled by the ocular hypotensive drug, but it resolved eventually by glaucoma filtration surgery (trabeculectomy). The elevation of intraocular pressure was attributed to the sub-Tenon's injection of depo-corticosteroid for treating ocular inflammation which occurred 11 days post-injection, and considered unrelated to Luxturna or the injection procedure.

In Studies 101 and 102 which spanned from Luxturna administration in Study 101 to the data cut-off on [redacted], 20[redacted] (Study 101/102), adverse events were reported in all subjects. All of the adverse events was considered causally unrelated to Luxturna. Table 24 shows adverse events reported in ≥30% of subjects.

Table 24. Adverse events reported in ≥30% of subjects (Study 101/102, safety analysis population, long-term follow-up [data cut-off on [redacted], 20[redacted]*])

	All subjects (N = 12)
Subjects with any adverse event	12 (100)
Conjunctival hyperaemia	8 (66.7)
Pyrexia	8 (66.7)
Nasopharyngitis	8 (66.7)
Headache	8 (66.7)
Leukocytosis	6 (50.0)
Abdominal discomfort	6 (50.0)
Influenza	6 (50.0)
Haematuria	6 (50.0)
Cataract	5 (41.7)
Contusion	5 (41.7)
Hypoglycaemia	5 (41.7)
Cough	5 (41.7)
Nausea	4 (33.3)
Ear infection	4 (33.3)
Blood creatinine increased	4 (33.3)
Hyperglycaemia	4 (33.3)
Proteinuria	4 (33.3)
Oropharyngeal pain	4 (33.3)

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n (%)
* Events reported during the period from the first dose of Luxturna to the data cut-off date of [redacted], 20[redacted] in Study 101. All subjects were followed up for >6 years after the first dose of Luxturna. Of them, 4 subjects were followed up for ≥10 years after the first dose of Luxturna.

The incidence of adverse events considered related to the injection procedure was 91.7% (11 of 12 subjects). Adverse events occurring in ≥2 subjects were conjunctival hyperaemia in 8 subjects, cataract in 4 subjects, dellen in 3 subjects, and intraocular pressure increased in 2 subjects.

No death occurred. Serious adverse events occurred in 5 subjects (intraocular pressure increased,[21)] lower limb fracture, cryptorchism, paraesthesia/colon adenoma, and anal fistula). All of the events were assessed as unrelated to Luxturna or the injection procedure, and resolved eventually.

7.1.1.3 Foreign phase III study (CTD 5.3.5.1-1, Study 301 [ongoing since November 2012 (data cut-off [redacted], 20[redacted])])

An open-label, randomized study was conducted at 2 study sites in the US to investigate the efficacy and safety of Luxturna in non-Japanese patients aged ≥3 years with biallelic *RPE65* mutation-associated IRD versus the untreated patients as the comparator (target sample size, 27 subjects[22)] [18 in the Luxturna group, 9 in the control group]).

Table 25 shows the main inclusion/exclusion criteria.

21) Events reported within 1 year after Luxturna administration in Study 102.
22) By assuming that the proportion of subjects showing ≥1 level of improvement in the primary endpoint, "change in the MLMT score using both eyes from baseline to 1 year after Luxturna administration to the second eye (at 1 year from baseline in the control group)," would be 80% in the Luxturna group and 20% in the control group, the statistical power was calculated to be 94% at the two-sided significance level of 5%, using a Wilcoxon's rank sum test.

Table 25. Main inclusion and exclusion criteria

Inclusion criteria	Patients who meet all of the following criteria: • Diagnosis of LCA due to biallelic *RPE65* mutation based on the of confirmation of molecular/genetic diagnosis by a CLIA-certified laboratory • ≥3 years of age • Visual acuity <20/60 for both eyes and/or visual field <20 degrees in any meridian, as measured by a III4e isopter or equivalent for both eyes. • Sufficient viable retinal cells must have either: 1) An area of retina within the posterior pole of >100 μm thickness shown on OCT 2) ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole 3) Remaining visual field within 30 degrees of fixation as measured by III4e isopter or equivalent • Evaluable on MLMT, as defined below: ➢ Patients who had an accuracy score* of ≤1 for MLMT at screening with the light level of ≤400 Lux ➢ Patients who were unable to pass MLMT at 1 Lux at the screening
Exclusion criteria	• Patients who previously participated in a study in which a gene therapy vector was administered • Patients who used retinoid compounds or precursors that could potentially interact with the biochemical activity of RPE65 protein within 18 months before screening visit • Patients with prior intraocular surgery within 6 months before screening visit • Patients with pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study

* Number of penalties/number of obstacles

Subjects confirmed to be eligible by the screening test were randomized to the Luxturna group and the control group in a 2:1 ratio, with stratification by age (≥10 years or <10 years) and the lowest light level allowing to navigate the course of the MLMT[23)] at the screening without problems (≥125 Lux or <125 Lux). Subjects assigned to the control group were eligible to cross over, after the first year of untreated follow-up, to receive Luxturna in the control/Luxturna group.

The study consisted of the following periods: (1) A screening period (90 days before baseline), (2) a baseline period (90 days before the day of the first-eye injection), (3) a treatment period (Luxturna group: after the baseline period, 6-18 days from the day of the first-eye injection to the day of the second-eye injection; control group: after the baseline period and the 12-month follow-up period, 6-18 days from the day of the first-eye injection to the day of the second-eye injection), and (4) a follow-up period (Luxturna group: 12 months after the second-eye injection; control group: 12 months after the baseline period, 12-month follow-up period, and the cross-over second-eye injection). At 1 year after Luxturna administration to the second eye ("Year 1"), subjects entered the long-term follow-up study (Study LTFU-01) after providing informed consent to be followed up for 15 years after Luxturna administration.

23) A test for the quantitative measurement of the functional vision in patients with biallelic *RPE65* mutation-associated IRD who have reduced light sensitivity and night blindness. The method was developed for assessment of this disease. The test assess the ability of the subject to navigate the assigned course accurately and at an appropriate speed under different light levels.

After vitrectomy, Luxturna was administered by subretinal injection at a dose of 1.5×10^{11} vg/300 µL to each eye at an interval of 12 ± 6 days.[24)] Subjects in the control group received Luxturna via subretinal injection after vitrectomy at a dose of 1.5×10^{11} vg/300 µL to each eye at an interval of 12 ± 6 days after the period from baseline to the completion of 1-year follow-up. In order to minimize inflammation associated with Luxturna injection procedures and to reduce immune response to the capsid protein of Luxturna and RPE65 protein, an oral systemic corticosteroid (prednisone) was administered according to the following dosage regimen:

- Prednisone was administered at 1 mg/kg/day (maximum of 40 mg/day) starting 3 days before the first-eye subretinal injection and continued for 7 days.
- In subjects receiving the second-eye subretinal injection within 12 days after the first-eye injection: Prednisone was given at 0.5 mg/kg/day (maximum of 20 mg/day) as a reduced dose for up to 5 days, followed by 1 mg/kg/day (maximum of 40 mg/day) as an increased dose starting 3 days before the second-eye subretinal injection and continued for 7 days. Subsequently, prednisone was given at 0.5 mg/kg/day (maximum of 20 mg/day) as a reduced dose for 5 days.
- In subjects receiving the second-eye subretinal injection >12 days after the first-eye injection: Prednisone was given at 0.5 mg/kg/day (maximum of 20 mg/day) as a reduced dose for 5 days, followed by 0.5 mg/kg every other day (maximum of 20 mg/day) until 3 days before the second-eye subretinal injection. Subsequently, prednisone was given at 1 mg/kg/day (maximum of 40 mg/day) as an increased dose starting 3 days before the subretinal injection and continued for 7 days, followed by 0.5 mg/kg/day (maximum of 20 mg/day) as a reduced dose for 5 days.

All of the 31 subjects enrolled in the study and randomized to either group (21 in the Luxturna group, 10 in the control group) were included in the intention-to-treat (ITT) population, and the ITT was used for the primary efficacy analysis. A total of 29 subjects (20 in the Luxturna group, 9 in the control group) were included in the safety analysis population. The remaining 2 subjects discontinued the study before they were informed of the group assigned (1 subject in the Luxturna group [investigator's discretion, without Luxturna injection], 1 subject in the control group [consent withdrawal]). No subjects discontinued the study after Luxturna administration. All subjects completed the assessment at 1 year after Luxturna administration to both eyes, and were undergoing the long-term follow-up at the data cut-off point. In the pooled analysis of the efficacy of subretinal administration of Luxturna in the Luxturna group and the control/Luxturna group, a total of 29 subjects (20 in the Luxturna group, 9 in the control/Luxturna group) were included in the modified intention-to-treat (mITT) population, and the mITT was used for the efficacy analysis. The remaining 2 subjects who dropped out from or discontinued the study before the assigned group was known to either of the subjects, the parents, the investigator, or the medical monitor were excluded from the analysis.

The primary endpoint in this study was the MLMT score using both eyes which was developed as a method to assess the subject's ability to navigate an assigned course accurately and at an appropriate speed under different light levels (Table 26).

[24)] To allow identification of surgical complications that might arise early after the first-eye subretinal injection before the second-eye subretinal injection and to minimize the risk of adverse immune responses associated with enhanced immune reactions to AAV that may occur if the second-eye injection is performed after a longer interval.

The outline of MLMT is as follows:

After 40 minutes of dark adaptation, the subject navigates a course avoiding obstacles and bumps placed on and along the course. The test proceeds from the lowest to higher light levels in a stepwise manner as shown in Table 26, in the order of one eye (the other eye is bandaged), the contralateral eye, and both eyes (without bandage). The test courses are assigned to each subject in a random manner, with the course configuration changed from test to test.

The MLMT score was based on the lowest light level under which the subject better navigated the course.

Table 26. Light level and brightness specified in MLMT and examples of environments corresponding to each MLMT score

Light level (lux)	Brightness (cd/m^2)		MLMT score	Corresponding environment
1 Lux	0.32	Twilight vision	6	Moonless summer night, or indoor nightlight
4 Lux	1.3	Twilight vision	5	Cloudless summer night with half-moon, or outdoor parking lot at night
10 Lux	3.2	Twilight vision	4	60 minutes after sunset in a city setting, or a bus stop at night
50 Lux	15.9	Photopic vision	3	Outdoor train station at night, or inside of illuminated office building stairwell
125 Lux	39.8	Photopic vision	2	30 minutes before cloudless sunrise, or interior of shopping mall, train, or bus at night
250 Lux	79.6	Photopic vision	1	Interior of elevator, library, or office hallway
400 Lux	127.3	Photopic vision	0	Office environment, or food court
>400 Lux*	>127.3	Photopic vision	−1	-

* Unable to navigate the MLMT course even at 400 Lux.

Table 27 shows the results of the primary efficacy endpoint, the mean change in the MLMT score using both eyes from baseline to Year 1 (i.e., 1 year after the second-eye injection).

Table 27. Mean change in MLMT score using both eyes from baseline to Year 1[*1] (Study 301, ITT population)

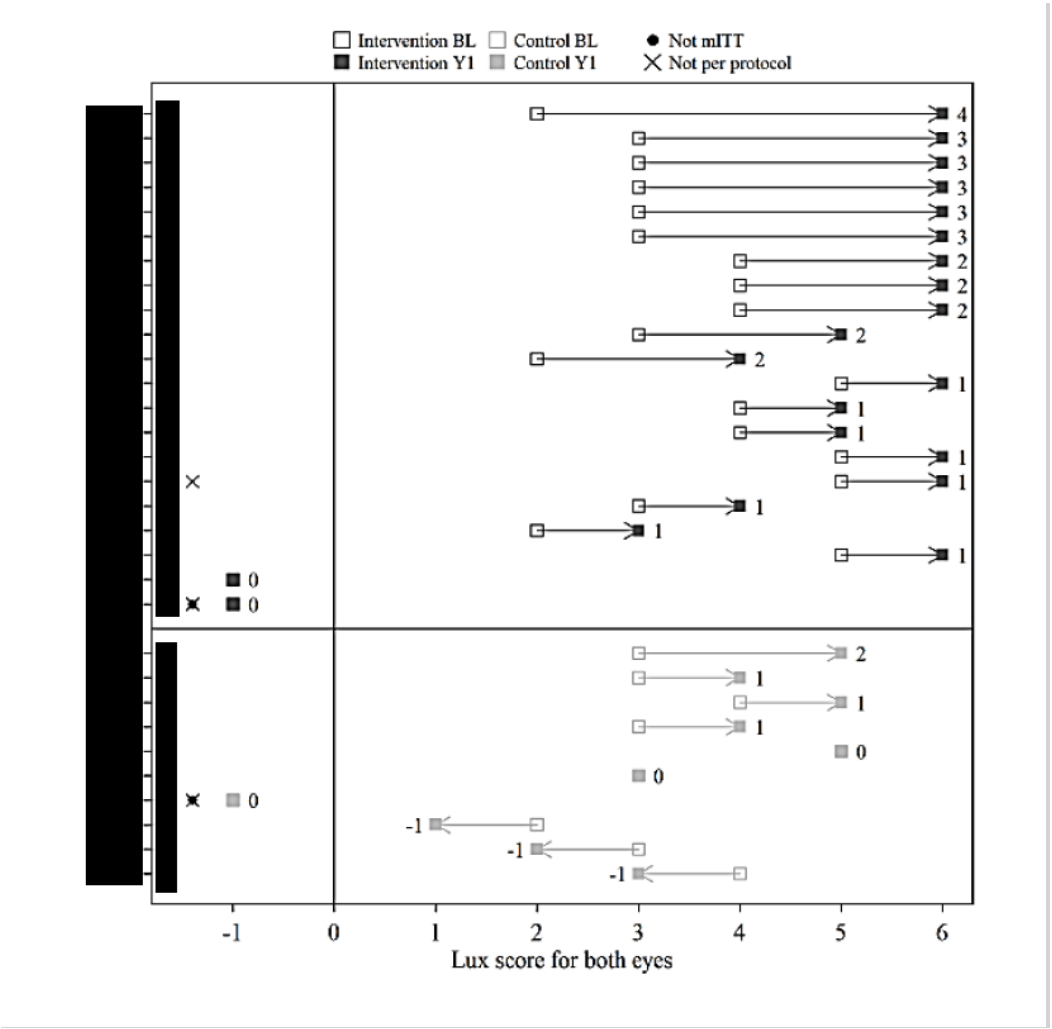
		Luxturna (n = 21)	Control (n = 10)
Baseline	Mean ± SD	3.1 ± 1.7	2.9 ± 1.6
	Range (min, max)	(−1, 5)	(−1, 5)
Change from baseline to Year 1	Mean ± SD	1.8 ± 1.1	0.2 ± 1.0
	Range (min, max)	(0, 4)	(−1, 2)
Between-group difference [95% CI] two-sided *P* value[*2]		1.6 [0.72, 2.41] 0.001	-

For subjects with missing data, the change from baseline to Year 1 was assumed to be 0.

*1 Up to 1 year from baseline in the control group

*2 Permutation test according to Wilcoxon rank sum test statistics with two-sided significance level of 5%

Figure 1 shows changes in the MLMT score using both eyes from baseline to Year 1 after second-eye injection (at 1 year from baseline in the control group) for individual subjects in both the Luxturna and control groups.

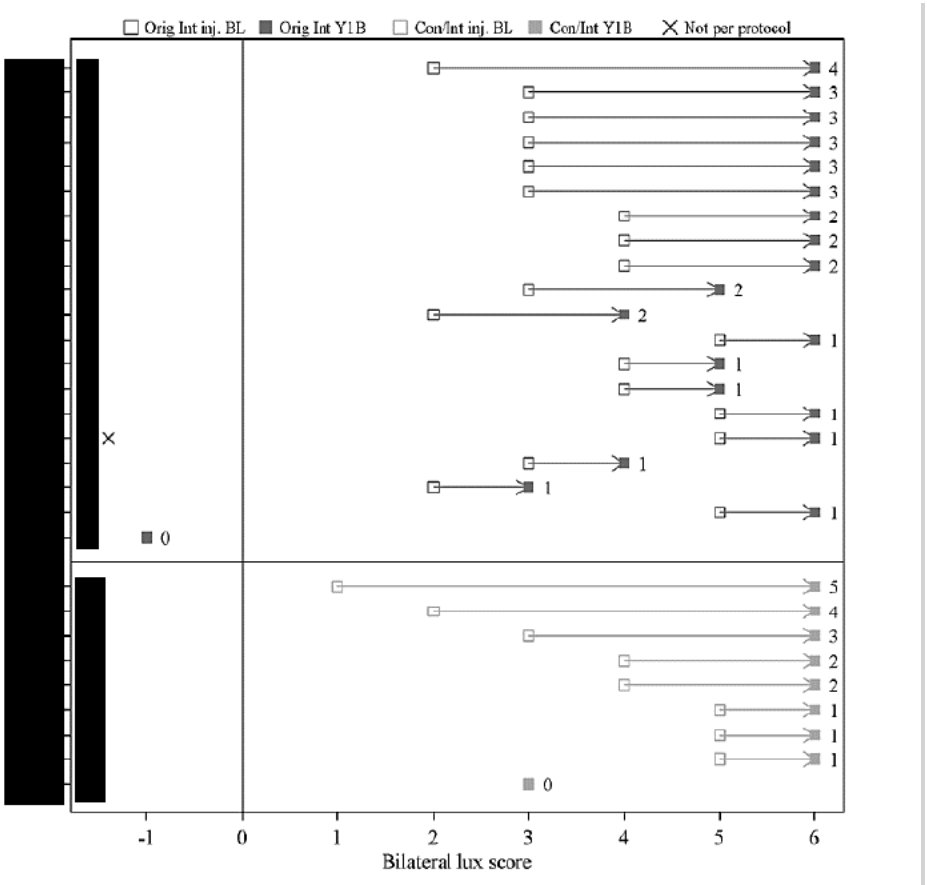


Intervention = Luxturna group; Control = Control group; BL = Baseline; Y1 = Year 1 after the second-eye injection

Figure 1. Change in MLMT score using both eyes from baseline to Year 1 after the second-eye injection for individual subjects in the Luxturna and control groups (at 1 year from baseline in the control group) (Study 301, ITT population)

Figure 2 shows changes in MLMT score using both eyes from baseline to Year 1 after the second-eye injection in both the Luxturna and control/Luxturna groups (from injection baseline in the control/Luxturna group[25)]). In the control/Luxturna group, the change (mean ± standard deviation [SD]) in MLMT score using both eyes from injection baseline to Year 1 after the second-eye injection was 2.1 ± 1.6, showing improvement comparable to that observed in the Luxturna group.

[25)] In the control/Luxturna group, the value measured before administration on the day of the first-eye injection was defined as "injection baseline." For subjects with multiple measured values within the allowable range of the day of the first-eye injection, the last value measured within the allowable range was used as the injection baseline. For subjects with no value measured before administration on the day of the first-eye injection, the value measured in the control group at 1 year from baseline was used as the injection baseline.



Orig Int = Luxturna; Con/Int = Control/Luxturna; inj. BL = Injection Baseline; Y1B = Year 1 after the second-eye injection

Figure 2. Change in MLMT score using both eyes from baseline to Year 1 after the-second eye injection for individual subjects in the Luxturna and control/Luxturna groups (Study 301, mITT population)

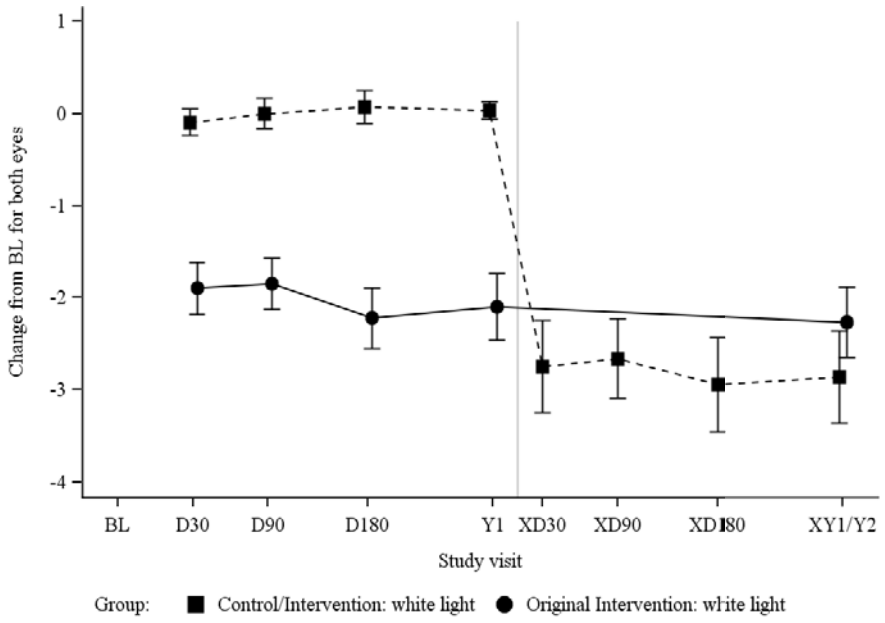
Table 28 shows the mean change in FST (mean of both eyes; white light; unit, log10 [cd.s/m^2]) from baseline to Year 1 after the second-eye injection.

Table 28. Mean change in FST (mean for both eyes; white light; unit, log10 [cd.s/m^2]) from baseline to Year 1 after the second-eye injection (Study 301, ITT population)

	Luxturna (n = 21)	Control (n = 10)
Baseline[*1]	−1.30 ± 0.43 (n = 20[*2])	−1.65 ± 0.35 (n = 9[*5])
1 year after administration[*1]	−3.37 ± 1.48 (n = 20[*3])	−1.61 ± 0.45 (n = 9[*5])
Change[*1]	−2.10 ± 1.58 (n = 19[*4])	0.04 ± 0.28 (n = 9[*5])
Median (range) of change	−1.71 (−5.61, 0.30)	−0.03 (−0.22, 0.69)

*1 Mean ± SD
*2 Handled as missing value because of the low credibility of the measured value in 1 subject ([redacted]).
*3 Missing value in 1 subject ([redacted]) who discontinued the study before subretinal administration
*4 Changes in FST were not evaluable in 2 subjects ([redacted]).
*5 Missing value in 1 subject ([redacted]) who discontinued the study before being informed of the assigned group

Figure 3 shows the time course in the mean change in FST (mean for both eyes; white light; unit, log10 [cd.s/m^2]) from baseline (injection baseline in the control/Luxturna group) to Year 1 after the second-eye injection. In the control/Luxturna group, the change in FST from injection baseline to Year 1 after the second-eye injection (mean ± SD) was −2.86 ± 1.49, showing improvement comparable to that observed in the Luxturna group.



Original Intervention = Luxturna; Control/Intervention = Control/Luxturna; BL = Baseline
D30, D90, D180, Y1, and Y2 = 30 days, 90 days, 180 days, 1 year, and 2 years after the second-eye injection in the Luxturna group
XD30, XD90, XD180, and XY1 = 30 days, 90 days, 180 days, and 1 year after the second-eye injection in the control/Luxturna group

Figure 3. Time course in the change in FST (mean for both eyes; white light; unit, log10 [cd.s/m^2]) (mean ± standard error [SE]) from baseline to Year 1 after the second-eye injection in the Luxturna and control/Luxturna groups (Study 301, mITT population)

Adverse events were reported in all subjects during the period from the first-eye injection to Year 1 after the second-eye injection (at 1 year from baseline in the control group). All of the adverse events were considered causally unrelated to Luxturna. Table 29 shows adverse events reported in ≥2 subjects in the Luxturna group.

Table 29. Adverse events reported in ≥2 subjects in the Luxturna group from the first-eye injection to Year 1 after the second-eye injection (Study 301, safety analysis population)

	Luxturna (N = 20)	Control (N = 9)
Subjects with any adverse event	20 (100)	9 (100)
Leukocytosis	9 (45.0)	0
Vomiting	8 (40.0)	2 (22.2)
Pyrexia	7 (35.0)	1 (11.1)
Nasopharyngitis	7 (35.0)	2 (22.2)
Headache	7 (35.0)	2 (22.2)
Nausea	6 (30.0)	1 (11.1)
Cough	6 (30.0)	1 (11.1)
Oropharyngeal pain	6 (30.0)	4 (44.4)
Intraocular pressure increased	4 (20.0)	0
Cataract	3 (15.0)	0
Haematuria	3 (15.0)	1 (11.1)
Eye inflammation	2 (10.0)	0
Retinal tear	2 (10.0)	0
Abdominal pain upper	2 (10.0)	0
Diarrhoea	2 (10.0)	1 (11.1)
Adverse drug reaction	2 (10.0)	0
Upper respiratory tract infection	2 (10.0)	3 (33.3)
Animal bite	2 (10.0)	0
Epistaxis	2 (10.0)	0
Nasal congestion	2 (10.0)	0

MedDRA ver.14.0
n (%)

No death occurred. Serious adverse events were reported in 2 subjects (convulsion/adverse drug reaction, adverse drug reaction) in the Luxturna group during the period from the first-eye injection to Year 1 after the second-eye injection. All of the events were considered causally unrelated to Luxturna or the injection procedure. The convulsion resolved with sequelae and both adverse drug reactions resolved without sequelae.

Table 30 shows the incidences of adverse events reported in ≥3 subjects treated with Luxturna in the entire population during the period from the first-eye injection to the data cut-off on [redacted], 20[redacted]. "Retinal deposits" (3 subjects) was the only Luxturna-related adverse event reported in the control/Luxturna group.

Table 30. Adverse events observed in ≥3 subjects among the entire subjects (Study 301, safety analysis population, long-term follow up [data cut-off on [redacted], 20[redacted]*])

	Luxturna (N = 20)	Control/Luxturna (N = 9)	Total (N = 29)
Subjects with any adverse event	20 (100)	9 (100)	29 (100)
Headache	7 (35.0)	6 (66.7)	13 (44.8)
Leukocytosis	9 (45.0)	2 (22.2)	11 (37.9)
Nausea	6 (30.0)	4 (44.4)	10 (34.5)
Vomiting	8 (40.0)	2 (22.2)	10 (34.5)
Pyrexia	8 (40.0)	2 (22.2)	10 (34.5)
Cataract	6 (30.0)	2 (22.2)	8 (27.6)
Nasopharyngitis	7 (35.0)	1 (11.1)	8 (27.6)
Cough	6 (30.0)	2 (22.2)	8 (27.6)
Oropharyngeal pain	6 (30.0)	1 (11.1)	7 (24.1)
Intraocular pressure increased	4 (20.0)	1 (11.1)	5 (17.2)
Nasal congestion	2 (10.0)	2 (22.2)	4 (13.8)
Retinal deposits	0	3 (33.3)	3 (10.3)
Retinal tear	2 (10.0)	1 (11.1)	3 (10.3)
Diarrhoea	3 (15.0)	0	3 (10.3)
Haematuria	3 (15.0)	0	3 (10.3)

MedDRA ver.23.0
n (%)
* In the Luxturna group, all subjects were followed up for 4 years after the second-eye injection, and of them, 8 subjects were followed up for 8 years after the second-eye injection. In the control/Luxturna group, all subjects were followed up for 2 years after the second-eye injection, and of them, 2 subjects were followed up for 7 years after the second-eye injection.

No death occurred during the period from the first-eye injection to the data cut-off on [redacted], 20[redacted]. Serious adverse events were reported in 6 subjects in the Luxturna group and in 2 subjects in the control/Luxturna group. The serious adverse events in the Luxturna group were convulsive seizure/adverse drug reaction/self-harm,[26)] adverse drug reaction, anembryonic gestation, ectopic pregnancy, menorrhagia/pneumonia/coronavirus disease 2019 (COVID-19) pneumonia, and retinal detachment,[27)] and those in the control/Luxturna group were acute myeloid leukaemia and retinal

[26)] The event name reported by the physician was entered because no preferred term is assigned to the event. A 1[redacted]-year-old (at enrollment) subject (gender = [redacted]). The subject was hospitalized for intentional self-injury (reported name, self-harm) approximately 8 years after Luxturna administration. The subject was discharged 10 days after hospitalization. The outcome was "resolved." The event was considered by the investigator and the sponsor to be unrelated to Luxturna or the injection procedure.

[27)] A [redacted]-year-old (at enrollment) subject (gender = [redacted]). At the Year 4 hospital visit, the subject complained of a decrease in visual acuity of the right eye starting approximately 7 months before. Examination revealed retinal detachment in the right eye which had not been recognized in the examination of the previous year. Diagnosis of retinal detachment (date of onset unknown) was made. The adverse event was moderate in severity and considered to be related to the injection procedure. Surgical treatment was performed, which resulted in slight improvement in the visual acuity of the right eye. The outcome was "resolved with sequelae."

fovea disorder.[28)] Retinal detachment in the Luxturna group and retinal fovea disorder in the control/Luxturna group were assessed as related to the injection procedures.

7.1.2 Japanese clinical study

7.1.2.1 Japanese phase III study (CTD 5.3.5.2-1, Study A11301 [Ongoing since November 2020 (data cut-off on [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted at a single study site in Japan to investigate the efficacy and safety of Luxturna in Japanese patients aged ≥4 years with biallelic *RPE65* mutation-associated IRD (target sample size, ≥1 subject and ≤4 subjects).

Table 31 shows main inclusion and exclusion criteria.

Table 31. Main inclusion and exclusion criteria

Inclusion criteria	Patients who met all of the following criteria: • Patients with biallelic *RPE65* mutation-associated IRD • ≥4 years of age • Visual acuity <20/60 (both eyes) and/or visual field <20 degrees in any meridian as measured by a III4e isopter or equivalent (both eyes). • Sufficient viable retinal cells fulfilling any of the following: 1) An area of retina within the posterior pole of >100 μm thickness shown on OCT 2) ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole 3) Remaining visual field within 30 degrees of fixation as measured by a III4e isopter or equivalent
Exclusion criteria	• Patients who previously participated in a study in which a gene therapy vector was administered. • Patients who used retinoid compounds or precursors (high-dose vitamin A supplement [daily dose >7,500 retinol equivalent or >3300 IU], isotretinoin, etc.) that could potentially interact with the biochemical activity of RPE65 protein within 6 months before screening visit. • Patients with prior intraocular surgery within 6 months before screening visit. • Patients who previously used any of medicines that, in the opinion of the investigator or the subinvestigator, potentially cause retinal damage (e.g., sildenafil or related compounds, hydroxychloroquine, chloroquine, thioridazine, and any other retino-toxic compounds). • Patient who used helenien within 1 month before the screening visit. • Patients with pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study.

The study consisted of a screening period (90 days before baseline), a baseline period (90 days before the first-eye injection), a treatment period (after the baseline period, 6-18 days from the day of the first-eye injection to the day of the second-eye injection), and a long-term follow-up period (5 years after the second-eye injection). The efficacy and safety of Luxturna were evaluated for 5 years after the second-eye injection.

Luxturna was administered by sequential subretinal injections to each eye at a dose of 1.5×10^{11} vg/300 μL after vitrectomy at an interval of 12 ± 6 days.[29)] In order to minimize inflammation

[28)] A 1[redacted]-year-old (at enrollment) subject (gender = [redacted]). The subject complained of a decrease in visual acuity in both eyes and blurred vision that had been persisting since the surgery for Luxturna administration. Thinning of the central fovea was confirmed in both eyes on Day 30 and Day 90 after Luxturna administration. FST showed improvement, while visual acuity decreased below the baseline value on Day 30 and decreased visual acuity persisted thereafter. No improvement was observed at the Year 1 visit, with the symptom in the right eye persisting stubbornly in particular. Based on the clinical course, a diagnosis of retinal fovea disorder in the right eye was made by the investigator (onset at 34 days after the first-eye injection [27 days after injection in the right eye]). The event was moderate in severity and assessed as related to the injection procedure. At the Year 1 hospital visit, the reduced visual acuity was stable without progression. The outcome of the event was "resolved with sequelae."

[29)] Luxturna was administered under general anesthesia and retrobulbar anesthesia to minimize eye movement during the surgery and postoperative discomfort. After subretinal injection of Luxturna, liquid-air exchange was conducted to remove Luxturna that may have flowed back from the site of subretinal injection (retinal opening) and to perform tamponade.

related to the injection procedure and to reduce immune responses to the capsid protein of Luxturna and RPE65 protein, an oral systemic corticosteroid (prednisolone) was administered.[30)]

All of the 4 subjects enrolled in the study received Luxturna. The 4 subjects were all included in the full analysis set (FAS), and the FAS was used for the safety analysis and the primary efficacy analysis. All subjects completed the Year 1 assessment of each eye without discontinuing the study. At the time point of the data cut-off, the long-term follow-up was still ongoing.

Table 32 shows the characteristics of individual subjects.

Table 32. Characteristics of individual subjects (Study A11301)

Subject ID	Age (years)	Sex	Clinical diagnosis	Eye complication(s) at enrollment	
[redacted]	4[redacted]	[redacted]	RP	Both eyes	Cataract
[redacted]	1[redacted]	[redacted]	LCA type 2	Both eyes	Nystagmus
[redacted]	1[redacted]	[redacted]	LCA type 2	Both eyes	Nystagmus
[redacted]	4[redacted]	[redacted]	RP	Both eyes	Cataract, dry eye

The efficacy endpoint, mean change (range) in FST (mean for both eyes; white light; unit, log10 [cd.s/m^2]) from baseline to Year 1 after the second-eye injection in the FAS, was −1.831 (−3.54 to −0.56) (Table 33).

Table 33. Change in FST (mean for both eyes; white light; unit, log10 [cd.s/m^2]) from baseline to Year 1 after the second-eye injection (Study A11301, FAS)

Subject ID	Baseline	Change from baseline to Year 1
[redacted]	−3.85	−0.61
[redacted]	−1.26	−3.54
[redacted]	−1.58	−2.62
[redacted]	−3.71	−0.56
Mean ± SD	−2.599 ± 1.3681	−1.831 ± 1.4910
Median (range)	−2.642 (−3.85, −1.26)	−1.613 (−3.54, −0.56)

Figure 4 shows changes over time in FST (mean for both eyes) measured by using optotypes in white light in individual subjects.

[30)] The dosage regimen of prednisolone was the same as that of prednisone in Study 301.

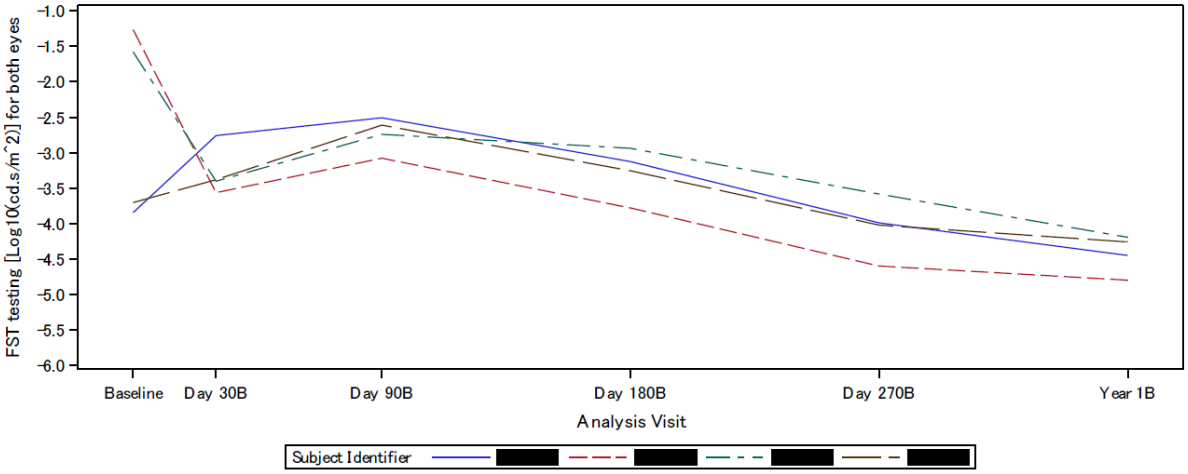


Figure 4. Changes over time in FST (mean for both eyes; white light; unit, log10 [cd.s/m^2]) from baseline to Year 1 after second-eye injection in individual subjects (Study A11301, FAS)

Tables 34, 35, and 36 show the results of visual acuity, kinetic visual field, and static visual field, defined as the secondary efficacy endpoints.

Table 34. Change in visual acuity from baseline to Year 1 after the second-eye injection (mean for both eyes; Lange scale; unit, logMAR) (Study A11301, FAS)

Subject ID	Baseline	Change from baseline to Year 1
[redacted]	2.15	−0.15
	1.11	−0.03
	1.41	−0.12
	1.80	0.17
Mean ± SD	1.616 ± 0.4553	−0.033 ± 0.1428
Median (range)	1.604 (1.11, 2.15)	−0.075 (−0.15, 0.17)

Table 35. Change in kinetic visual field from baseline to Year 1 after the second-eye injection (mean of both eyes, Goldmann visual field perimetry, total degrees across 24 meridians) (Study A11301, FAS)

	Target size: III4e		Target size: V4e	
Subject ID	Baseline	Change from baseline to Year 1	Baseline	Change from baseline to Year 1
[redacted]	0	3	38	127
	119	705	1318	46
	586	1014	1112	647
	53	−11	213	−18
Mean ± SD	189.5 ± 268.78	427.8 ± 514.29	670.0 ± 638.91	200.5 ± 303.52
Median (range)	86.0 (0, 586)	354.0 (−11, 1014)	662.3 (38, 1318)	86.5 (−18, 647)

Table 36. Change in static visual field from baseline to Year 1 after the second-eye injection (mean or both eyes; Humphrey automated perimetry; unit, dB) (Study A11301, FAS)

	Foveal sensitivity		Macula threshold	
Subject ID	Baseline	Change from baseline to Year 1	Baseline	Change from baseline to Year 1
[redacted]	0	0.59	2.56	−2.56
	13.37	9.63	16.50	2.87
	15.15	6.00	16.50	3.50
	3.00	−1.29	2.16	−0.66
Mean ± SD	7.880 ± 7.5034	3.734 ± 4.9991	9.428 ± 8.1683	0.790 ± 2.8837
Median (range)	8.185 (0, 15.15)	3.295 (−1.29, 9.63)	9.528 (2.16, 16.50)	1.108 (−2.56, 3.50)

Adverse events were reported in all 4 subjects during the period from the first-eye injection to Year 1 after the second-eye injection. The reported events[31)] were white blood cell count increased in 4 subjects; eye pain and constipation in 2 subjects each; dry eye, abdominal pain, vomiting, pyrexia, ankle fracture, intraocular pressure increased, myalgia, ovarian cyst torsion, acne, and dry skin in 1 subject each. All of the events were considered causally unrelated to Luxturna.

All 4 subjects experienced adverse events assessed as related to perioperative corticosteroid use, which were white blood cell count increased in 4 subjects and constipation in 2 subjects.

No death occurred. A serious adverse event (ovarian cyst torsion) was reported in 1 subject. This event was assessed as unrelated to the administration of Luxturna, the injection procedure, or perioperative corticosteroid use. The outcome of the event was "resolved."

7.R Outline of the review conducted by PMDA

7.R.1 Use of foreign clinical study data and review policy

For the present application, results of the following 3 foreign clinical studies were submitted as evaluation data: 2 foreign phase I studies (Studies 101 and 102) and 1 foreign phase III study (Study 301) that investigated the efficacy and safety of Luxturna in non-Japanese patients with biallelic *RPE65* mutation-associated IRD, whereas data from only 4 Japanese subjects were submitted as the results of the Japanese phase III study (Study A11301).

The applicant's explanation about the appropriateness of evaluating the efficacy and safety of Luxturna in Japanese patients based mainly on the result of the foreign clinical studies:
Study A11301 was conducted as an open-label, uncontrolled study involving a limited number of subjects, taking account of its feasibility, because of the very small number of Japanese patients eligible for treatment with Luxturna. Accordingly, the efficacy and safety of Luxturna in Japanese patients were evaluated based on the results of foreign Studies 101, 102, and 301 conducted to investigate the efficacy and safety of Luxturna, in addition to the results of Study A11301.

As described below, there seem to be no intrinsic or extrinsic ethnic factors affecting the efficacy or safety of Luxturna, and it is therefore acceptable to evaluate the efficacy and safety of Luxturna in Japanese patients based on the results of the foreign clinical studies.

(a) Intrinsic ethnic factors

- There are no significant differences between Japanese and non-Japanese patients either in the size of eyeballs or in the structure of the posterior eye segment, retinal thickness in particular, that directly affects the subretinal administration of Luxturna (*Transl Vis Sci Technol.* 2020;9:2, *Invest Ophthalmol Vis Sci.* 2010;51:2644-7, *Invest Ophthalmol Vis Sci.* 2010;51:465-73, etc.).
- The biochemistry of the visual (retinoid) cycle is common among vertebrates (*Chem Rev.* 2014;114:194-232).

31) MedDRA ver. 25.0

(b) Diagnosis and treatment policy (extrinsic ethnic factors)

- There is no difference in the method for diagnosing biallelic *RPE65* mutation-associated IRD between Japan and foreign countries (*Int J Mol Sci.* 2021;22:7207, *Ophthalmic Genetics.* 2016;37:161-9, *J Jpn Ophthalmol Soc.* 2020;124:247-84)
- There is no established treatment of biallelic *RPE65* mutation-associated IRD other than Luxturna in foreign countries.
- There is no significant difference between Japan and foreign countries in the surgical equipment, instruments, or procedures used in vitrectomy prior to the subretinal administration of Luxturna, nor is there any difference in the safety of vitrectomy between Japan and foreign countries (American Academy of Ophthalmology [https://www.aao.org/focalpointssnippetdetail.aspx?id=af56d760-dd05-4399-ad95-b26636f5fc0c (last accessed on May 17, 2022)], *Retina.* 2017;37:2130-7).
- Subretinal administration is a practice commonly used safely in Japan as well (*Retina.* 2016;36:1035-8, *PLoSOne.* 2017;12:e0177241).

(c) Characteristic features of Luxturna insusceptible to ethnic factors

- Luxturna exerts its effect by complementing RPE65 protein regardless of the difference in the mutations of the *RPE65* gene that is the cause of biallelic *RPE65* mutation-associated IRD.
- Since Luxturna is a recombinant AAV that is topically injected directly into the target therapeutic site at the posterior segment of the eye, the exposure to Luxturna is not affected by metabolic enzymes or transporters.

PMDA accepted the above explanation of the applicant.

7.R.2 Efficacy

Based on the review in the subsections below, PMDA has concluded that Luxturna was shown to have a certain level of efficacy in the treatment of patients with biallelic *RPE65* mutation-associated IRD.

7.R.2.1 Reason for conducting Study 301 designed as an open-label study

The applicant's explanation:

Study 301 designed as an open-label study was appropriate, for the following reasons:

- Use of a sham-subretinal injection group (sham group) as the comparator is ethically infeasible because of the risk of surgical complications such as infection, and because of children included in the study subjects.
- The primary endpoint, MLMT, is assessed by a blinded independent observer, allowing objective efficacy assessment.

PMDA concluded that the applicant's explanation is understandable and Study 301 designed as an open-label study was acceptable.

7.R.2.2 Appropriateness of primary efficacy endpoint

The applicant's explanation about the MLMT scores using both eyes as the primary endpoint in Study 301 and FST (mean of both eyes, optotypes in white light) as the primary endpoint in Study A11301:

Study 301

The most updated US Food and Drug Administration (FDA) guidance "Human Gene Therapy for Retinal Disorders, 2020" recommends measurement of both visual function[32)] and functional vision[33)] in clinical studies on cell therapy and gene therapy for retinal disorder. Accordingly, based on the discussion with the FDA, the applicant developed MLMT as a method for quantitatively measuring the functional vision of patients with biallelic *RPE65* mutation-associated IRD. MLMT measures the subject's ability to navigate an assigned course accurately at a reasonable speed under different light levels. Among MLMT scores, the MLMT score using both eyes was selected as the primary endpoint that most closely reflects the actual clinical state of the patient.

A non-interventional, observational study (Mobility Test Validation Study [MTVS study]) was conducted to validate MLMT (*Clin Exp Ophthalmol.* 2018;46:247-59). In MTVS study, change from baseline in the MLMT score using both eyes at 1-Year Visit was 0 (no change) in all of 26 subjects with normal vision, whereas in subjects with impaired vision (including 1 patient with biallelic *RPE65* mutation-associated IRD), the change was 0 (no change) in 20 of 28 subjects (71%) and −1 to −2 (aggravated) in the remaining 8 subjects (29%). All 8 subjects showing aggravation had been diagnosed with LCA or RP. In the subject diagnosed with biallelic *RPE65* mutation-associated IRD, the change was −1 (aggravated). These results, together with the fact that biallelic *RPE65* mutation-associated IRD is a progressive retinal degenerative disease, show that the MLMT score does not improve by spontaneous course of the disease.

Study A11301

Initially, the applicant had planned to conduct Study A11301 using MLMT as the primary endpoint as was the case with Study 301, but eventually considered that this plan was infeasible in Japan, for the following reasons: (1) Since [redacted] of MLMT was [redacted] by [redacted], only 2 study sites, which had joined Study 301, were allowed to conduct the same MLMT as performed in Study 301; and (2) it was infeasible to relocate the test facility to other sites. Instead, FST (mean for both eyes, white light), albeit unable to serve as an index for functional vision, was used as the primary endpoint that allows quantitative measurement of light sensitivity related to functional vision because FST was evaluated as a secondary endpoint in Study 301 and thought to be correlated with MLMT.

FST allows evaluation of light sensitivity of the entire retina. It is an appropriate index for evaluating night blindness, the primary symptom of patients with biallelic *RPE65* mutation-associated IRD, because (i) FST is not affected by nystagmus, a complication frequently experienced by patients with biallelic *RPE65* mutation-associated IRD; and (ii) FST can be assessed regardless of vision disorder or its severity. In addition, compared with other colors, white light is best suited for the measurement of

32) Indicates how well the eye and visual system function.
33) Indicates how well the patient performs vision-related activities of daily living.

rod function which is mainly impaired in patients with biallelic *RPE65* mutation-associated IRD (*Exp Eye Res.* 2005;80:259-72).

PMDA's view:
The applicant's explanation about the use of the MLMT score using both eyes as the primary endpoint of Study 301 is acceptable. Although it would have been desirable to use MLMT as the primary endpoint in Study A11301 as well, given the difficulty in conducting MLMT in Japan, it is acceptable to use FST (mean for both eyes, white light) as the primary endpoint of Study A11301 because FST is an index appropriate for assessing light sensitivity, an impaired function in patients with biallelic *RPE65* mutation-associated IRD.

On the other hand, not only MLMT and FST but also visual acuity and visual field are important for the evaluation of the therapeutic effect against biallelic *RPE65* mutation-associated IRD. Accordingly, the efficacy of Luxturna was evaluated mainly based on MLMT and FST, the primary endpoint used in each study, and on visual acuity and visual field as the auxiliary indices.

7.R.2.3 Results of efficacy evaluation

The applicant's explanation about the efficacy of Luxturna in patients with biallelic *RPE65* mutation-associated IRD:
In Study 301, the between-group difference [95% confidence interval (CI)] in mean change in the MLMT score using binocular vision (both eyes) from baseline to Year 1 after the second-eye injection (at 1 year from baseline in the control group), the primary endpoint, was 1.6 [0.72, 2.41], showing a statistically significant between-group difference and an improvement of ≥1, the value considered clinically significant (see Table 27). The between-group difference [95% CI] in mean change in the MLMT score using monocular vision, the secondary endpoint, was 1.7 [0.89, 2.52] in the first-treated eye and 2.0 [1.14, 2.85] in the second-treated eye, showing a difference similar to that in the MLMT score using binocular vision.

The change (mean ± SD) (log10 [cd.s/m^2]) in FST (mean for both eyes, white light) from baseline to Year 1 after the second-eye injection (at 1 year from baseline in the control group) in Study 301 was −2.10 ± 1.58 in the Luxturna group (19 subjects) and 0.04 ± 0.28 in the control group (9 subjects), with the between-group difference [95% CI] (log10 [cd.s/m^2]) of the mean change being −2.13 [−3.23, −1.03]. The between-group difference [95% CI] of the mean change in FST (monocular, white light) (log10 [cd.s/m^2]) was −2.38 [−3.50, −1.25] in the first-treated eye and −1.89 [−3.06, −0.72] in the second-treated eye, showing a similar difference to that in FST for binocular vision.

In the pooled analysis of data from the Luxturna group and the control/Luxturna group, the change in FST from baseline (injection baseline in the control/Luxturna group) to Year 1 after the second-eye injection was a decrease of ≥2 log10 (cd.s/m^2), which was greater than the clinically significant threshold (1 log10 [cd.s/m^2]) (*Lancet.* 2017;390:849-60), in 16 of 28 evaluable subjects (9 of 19 subjects in the Luxturna group, 7 of 9 in the control/Luxturna group), showing a ≥100-fold improvement in light sensitivity. FST decreased by ≥1 log10 (cd.s/m^2) in 21 of 28 evaluable subjects (13 of 19 subjects in the Luxturna group, 8 of 9 subjects in the control/Luxturna group). All of the 21

subjects showed improvement of ≥1 in the MLMT score using both eyes from baseline, which is greater than the threshold of clinically significant improvement. Of the 21 subjects, 20 achieved the MLMT score of 6 (maximum score). This result suggested a correlation (correlation coefficient −0.58) between the results of the MLMT score using both eyes and FST (mean of both eyes, white light) during this period.

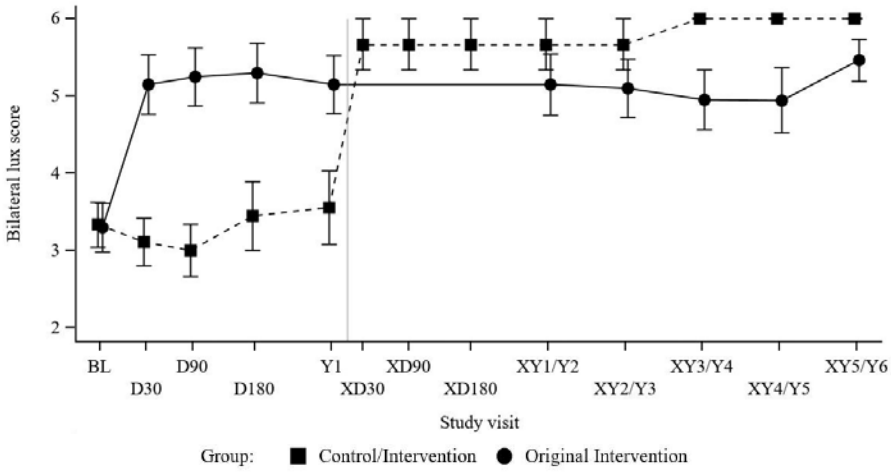
In Study A11301, the mean change (range) in FST (mean for both eyes, white light) from baseline to Year 1 after the second-eye injection was −1.831 (−3.54 to −0.56) log10 (cd.s/m^2), showing a decrease (improvement) in FST from baseline (Table 33). During this period, the change from baseline in FST in all subjects was greater than 0.3 log10 (cd.s/m^2), the value regarded as the limit of variation in multiple measurements (*Doc Ophthalmol.* 2009;119:217-24, *Clin Exp Optom.* 2014;97:240-7). In 2 of 4 subjects, FST decreased by ≥2 log10 (cd.s/m^2), a greater value than the clinically significant threshold of 1 log10 (cd.s/m^2) (*Lancet.* 2017;390:849-60), showing ≥100-fold improvement in light sensitivity.

Results of visual acuity and visual field tests in Study 301 were as follows:

- Visual acuity (mean for both eyes, Holladay scale):
  In the Luxturna group, some subjects (7 of 21 subjects for the first-treated eye and 4 of 21 subjects for the second-treated eye) showed improvement in visual acuity from baseline to Year 1 after the second-eye injection, which was not less than 0.3 logMAR, the clinically significant value (*Invest Ophthalmol Vis Sci.* 2017;58:3456-63, *Invest Ophthalmol Vis Sci.* 2008;49:479-89). In the control group, no subjects showed improvement of ≥0.3 logMAR.
- Kinetic visual field measured by Goldmann visual field perimetry (mean for both eyes; target size, III4e):
  The between-group difference [95% CI] in the mean change in the sum total degrees of visual fields calculated across 24 meridians from baseline to Year 1 after the second-eye injection was 378.7 [145.5, 612.0], showing a greater improvement in the Luxturna group than in the control group. In the Luxturna group, the mean value of the sum total degrees for the 24 meridians increased by approximately 91% from baseline to Year 1 after the second-eye injection, exceeding the threshold for the range of variation in multiple measurements (20%) (*Invest Ophthalmol Vis Sci.* 2011;52:8042-6).
- Static visual field measured by Humphrey automated perimeter (mean for both eyes, macula threshold):
  The between-group difference [95% CI] in the mean change from baseline to Year 1 after the second-eye injection was 7.9 [3.5, 12.2] dB, showing a greater improvement in the Luxturna group than in the control group. In the Luxturna group, the mean change in the macula threshold from baseline to Year 1 after the second-eye injection was greater than 4 dB, the clinically significant change (*Br J Ophthalmol.* 2022; in press), demonstrating the improvement in retinal sensitivity.
- Static visual field measured by Humphrey automated perimeter (mean for both eyes, foveal sensitivity):
  The improvement in the foveal sensitivity from baseline was marginal in the Luxturna group as well.

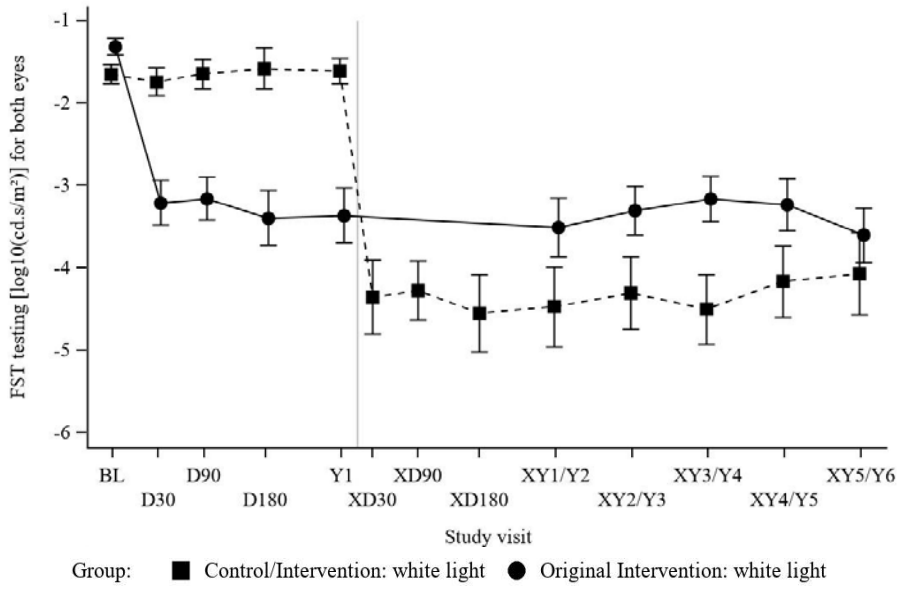
Given that Luxturna acts mainly on rod cells, it is not expected to improve visual acuity or foveal sensitivity, functions mediated by pyramidal cells. However, in patients with biallelic *RPE65* mutation-associated IRD who show a marked progressive decrease and severe loss of visual acuity, even a slight increase in visual acuity is considered to contribute to improvement in vision-related activities of daily life.

Data on the long-term efficacy of Luxturna were evaluated. Figures 5 and 6 show changes over time in the MLMT score using both eyes and FST in Study 301 (data cut-off on [redacted], 20[redacted]).



Original Intervention = Luxturna; Control/Intervention = Control/Luxturna; BL = Baseline
D30, D90, D180, and Y1 to Y6 = 30 days, 90 days, 180 days, and 1 to 6 years after the second-eye injection in the Luxturna group
XD30, XD90, XD180, and XY1 to XY5 = 30 days, 90 days, 180 days, and 1 to 5 years after the second-eye injection in the control/Luxturna group

Figure 5. Changes over time in MLMT score using both eyes (mean ± SE) from baseline to Year 6 after the second-eye injection in the Luxturna group and those from baseline to Year 5 after the second-eye injection in the control/Luxturna group
(Study 301, mITT population, data cut-off on [redacted], 20[redacted])



Original Intervention = Luxturna; Control/Intervention = Control/Luxturna; BL = Baseline
D30, D90, D180, and Y1 to Y6 = 30 days, 90 days, 180 days, and 1 to 6 years after the second-eye injection in the Luxturna group
XD30, XD90, XD180, and XY1 to XY5 = 30 days, 90 days, 180 days, and 1 to 5 years after the second-eye injection in the control/Luxturna group

Figure 6. Changes over time in FST (mean for both eyes; white light; unit, log10 (cd.s/m^2) (mean ± SE) from baseline to Year 6 after the second-eye injection in the Luxturna group and those from baseline to Year 5 after the second-eye injection in the control/Luxturna group (Study 301, mITT population, data cut-off on [redacted])

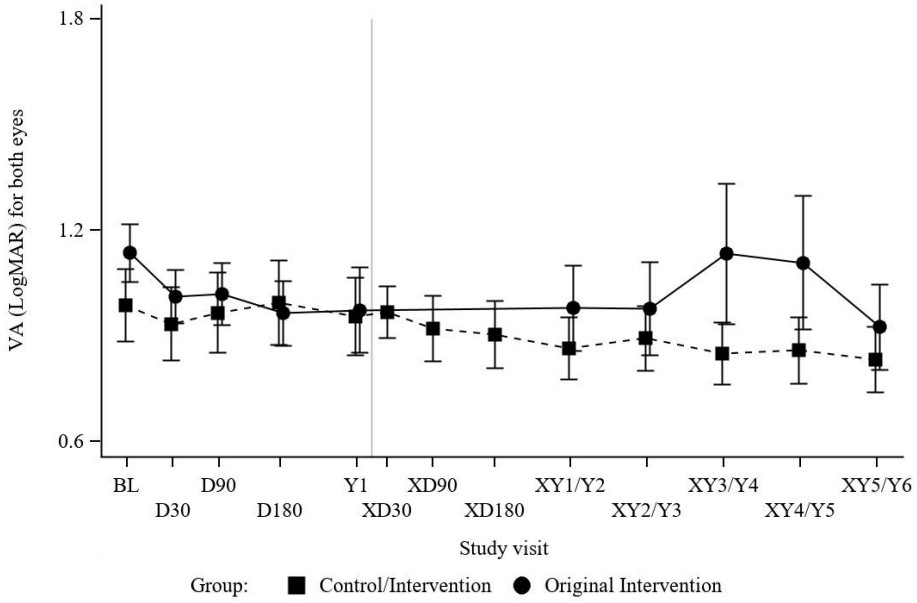
Figures 7 to 11 show changes over time in visual acuity, kinetic visual field, and static visual field (mean for both eyes).

Visual acuity:

In the Luxturna group, subjects showed a sustained improvement for approximately 6 years after the second-eye injection, but had a transient worsening at Year 4 and 5. This was considered due to the results of 2 subjects who showed deterioration of visual acuity caused by adverse events (retinal detachment and macular fibrosis). In the control/Luxturna group, the change in visual acuity after Luxturna administration was minimal compared to that in the Luxturna group, but visual acuity gradually improved from injection baseline to Year 5 after the second-eye injection.

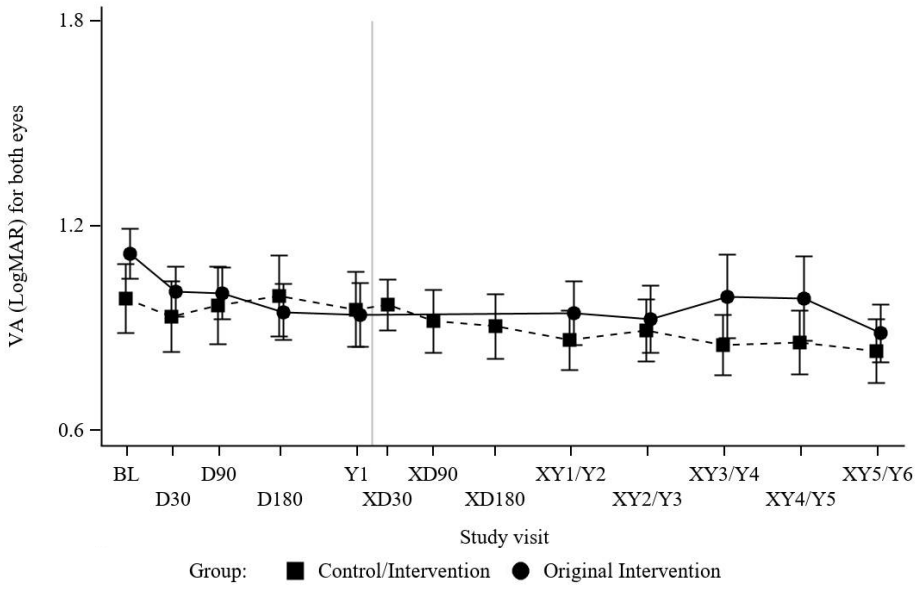
Visual field:

The results for the kinetic visual field (mean for both eyes; Goldmann visual field perimetry; target size, III4e; sum total degrees for the 24 meridians) and the static visual field (mean for both eyes, Humphrey automated perimeter, macula threshold) showed sustained improvement, while the improvement in the static visual field (mean for both eyes, Humphrey automated perimeter, foveal sensitivity) was minimal. As is the case with visual acuity, Luxturna may not improve foveal sensitivity which is a pyramidal cell-mediated function.



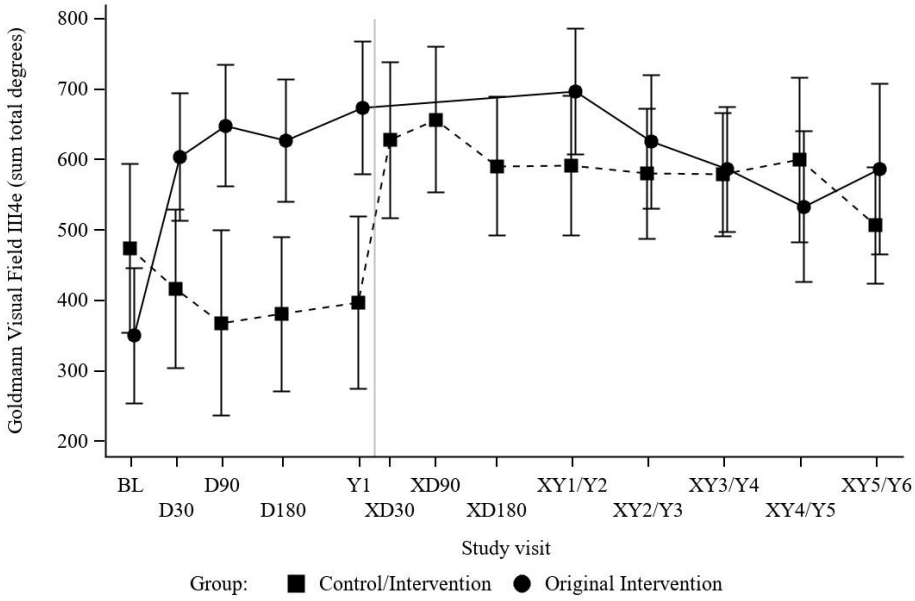
Original Intervention = Luxturna; Control/Intervention = Control/Luxturna; BL = Baseline
D30, D90, D180, and Y1 to Y6 = 30 days, 90 days, 180 days, and 1 to 6 years after the second-eye injection in the Luxturna group
XD30, XD90, XD180, and XY1 to XY5 = 30 days, 90 days, 180 days, and 1 to 5 years after the second-eye injection in the control/Luxturna group

Figure 7. Changes over time in visual acuity (mean for both eyes; Holladay scale; unit, logMAR) (mean ± SE) from baseline to Year 6 after the second-eye injection in the Luxturna group and those from baseline to Year 5 after the second-eye injection in the control/Luxturna group (Study 301, mITT population, data cut-off on [redacted])



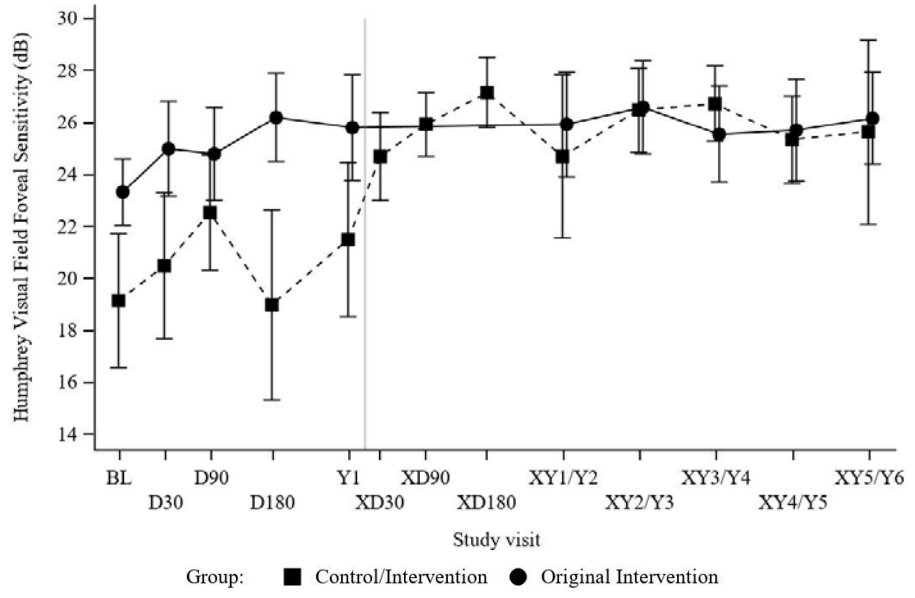
Original Intervention = Luxturna; Control/Intervention = Control/Luxturna; BL = Baseline
D30, D90, D180, and Y1 to Y6 = 30 days, 90 days, 180 days, and 1 to 6 years after the second-eye injection in the Luxturna group
XD30, XD90, XD180, and XY1 to XY5 = 30 days, 90 days, 180 days, and 1 to 5 years after the second-eye injection in the control/Luxturna group

Figure 8. Changes over time in visual acuity (mean for both eyes; Lange scale; unit, logMAR) (mean ± SE) from baseline to Year 6 after the second-eye injection in the Luxturna group and those from baseline to Year 5 after the second-eye injection in the control/Luxturna group (Study 301, mITT population, data cut-off on [redacted])



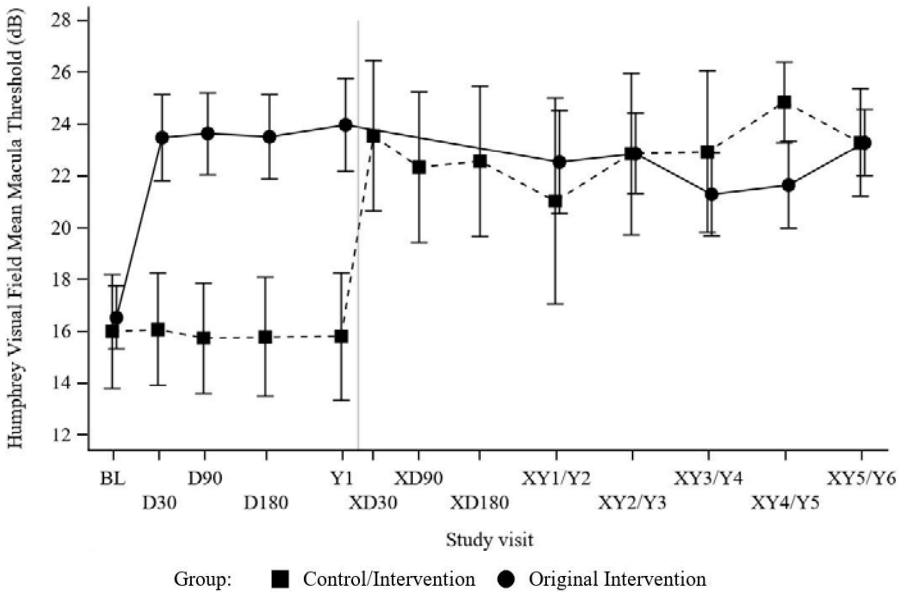
Original Intervention = Luxturna; Control/Intervention = Control/Luxturna; BL = Baseline
D30, D90, D180, and Y1 to Y6 = 30 days, 90 days, 180 days, and 1 to 6 years after the second-eye injection in the Luxturna group
XD30, XD90, XD180, and XY1 to XY5 = 30 days, 90 days, 180 days, and 1 to 5 years after the second-eye injection in the control/Luxturna group

Figure 9. Changes over time in kinetic visual field (mean for both eyes, Goldmann visual field perimetry, target size: III4e, sum total degrees for the 24 meridians) (mean ± SE) from baseline to Year 6 after the second-eye injection in the Luxturna group and those from baseline to Year 5 after the second-eye injection in the control/Luxturna group
(Study 301, mITT population, data cut-off on [redacted], 20[redacted])



Original Intervention = Luxturna; Control/Intervention = Control/Luxturna; BL = Baseline
D30, D90, D180, and Y1 to Y6 = 30 days, 90 days, 180 days, and 1 to 6 years after the second-eye injection in the Luxturna group
XD30, XD90, XD180, and XY1 to XY5 = 30 days, 90 days, 180 days, and 1 to 5 years after the second-eye injection in the control/Luxturna group

Figure 10. Changes over time in static visual field (mean of both eyes, Humphrey automated perimeter, foveal sensitivity, unit, dB) (mean ± SE) from baseline to Year 6 after the second-eye injection in the Luxturna group and those from baseline to Year 5 after the second-eye injection in the control/Luxturna group (Study 301, mITT population, data cut-off on [redacted], 20[redacted])



Original Intervention = Luxturna; Control/Intervention = Control/Luxturna; BL = Baseline
D30, D90, D180, and Y1 to Y6 = 30 days, 90 days, 180 days, and 1 to 6 years after the second-eye injection in the Luxturna group
XD30, XD90, XD180, and XY1 to XY5 = 30 days, 90 days, 180 days, and 1 to 5 years after the second-eye injection in the control/Luxturna group

Figure 11. Changes over time in static visual field (mean for both eyes, Humphrey automated perimeter, macula threshold, unit, dB) (mean ± SE) from baseline to Year 6 after the second-eye injection in the Luxturna group and those from baseline to Year 5 after the second-eye injection in the control/Luxturna group (Study 301, mITT population, data cut-off on [redacted], 20[redacted])

The effect of age difference on the efficacy of Luxturna was investigated. Table 37 shows the results of efficacy endpoints in Study 301, classified by age group. At baseline (injection baseline in the control/Luxturna), the MLMT score using both eyes, visual acuity, and visual field in subjects aged ≥18 years were inferior to those in subjects aged <18 years.

The change in the MLMT score using both eyes (mean ± SD) from baseline (injection baseline in the control/Luxturna group) to Year 1 after the second-eye injection was 1.7 ± 1.6 in subjects aged ≥18 years (n = 9) and 2.1 ± 1.1 in subjects aged <18 years (n = 20). The change (mean ± SD) in FST (mean for both eyes; white light; unit, log10 [cd.s/m^2]) was −1.35 ± 1.41 in subjects aged ≥18 years (n = 9) and −2.81 ± 1.44 in subjects aged <18 years (n = 19), showing approximately 10-fold and 1,000-fold improvement in light sensitivity, respectively. Visual field and visual acuity also markedly improved in subjects aged <18 years compared to subjects aged ≥18 years. In particular, whereas the change in visual acuity (mean for both eyes; Lange scale; unit, logMAR) (mean ± SD) was −0.01 ± 0.23 in subjects aged ≥18 years (n = 9), showing an improvement by 0.5 letters on the early treatment diabetic retinopathy study (ETDRS) chart, the change in subjects aged <18 years (n = 20) was −0.21 ± 0.17, showing an improvement equivalent to 10.5 letters on the ETDRS chart.

Table 37. Efficacy by baseline age (Study 301, mITT population)

		<18 years of age	≥18 years of age
MLMT score using both eyes			
Baseline	Mean ± SD	3.8 ± 1.0 (n = 20)	2.4 ± 1.7 (n = 9)
	Median (range)	4 (2, 5)	3 (−1, 5)
Change from baseline to Year 1	Mean ± SD	2.1 ± 1.1 (n = 20)	1.7 ± 1.6 (n = 9)
	Median (range)	2 (1, 4)	1 (0, 5)
FST (mean for both eyes; white light; unit, log10 [cd.s/m^2])			
Baseline	Mean ± SD	−1.34 ± 0.47 (n = 19)	−1.57 ± 0.42 (n = 9)
	Median (range)	−1.43 (−2.14, −0.13)	−1.57 (−2.20, −0.95)
Change from baseline to Year 1	Mean ± SD	−2.81 ± 1.44 (n = 19)	−1.35 ± 1.41 (n = 9)
	Median (range)	−2.82 (−5.61, −0.62)	−0.77 (−3.80, 0.30)
Visual acuity (mean for both eyes; Lange scale; unit, LogMAR)			
Baseline	Mean ± SD	0.97 ± 0.22 (n = 20)	1.28 ± 0.44 (n = 9)
	Median (range)	0.94 (0.70, 1.63)	1.27 (0.52, 1.87)
Change from baseline to Year 1	Mean ± SD	−0.21 ± 0.17 (n = 20)	−0.01 ± 0.23 (n = 9)
	Median (range)	−0.17 (−0.61, 0.07)	−0.11 (−0.27, 0.37)
Kinetic visual field (mean for both eyes, Goldmann perimeter, target size: III4e, sum total degrees for the 24 meridians)			
Baseline	Mean ± SD	421.4 ± 410.6 (n = 19)	247.9 ± 354.2 (n = 9)
	Median (range)	242 (45, 1418)	105 (0, 1144)
Change from baseline to Year 1	Mean ± SD	358.4 ± 269.6 (n = 19)	75.3 ± 180.8 (n = 9)
	Median (range)	392 (−59, 820)	19 (−215, 396)
Static visual field (mean for both eyes; Humphrey automated perimeter; macula threshold; unit, dB)			
Baseline	Mean ± SD	17.78 ± 5.29 (n = 19)	13.22 ± 6.28 (n = 9)
	Median (range)	17.2 (8.1, 26.3)	12.9 (1.9, 23.5)
Change from baseline to Year 1	Mean ± SD	10.24 ± 4.73 (n = 19)	−0.22 ± 7.51 (n = 9)
	Median (range)	9.3 (1.7, 18.9)	1.3 (−12.3, 13.1)

The applicant's explanation about the efficacy of Luxturna in Japanese patients:
The efficacy of Luxturna in Japanese patients was evaluated based on the comparison of data between Study A11301 and Study 301.

Tables 38 and 39 show the baseline characteristics of patients (injection baseline in the control/Luxturna group in Study 301) in Studies A11301 and 301.

Age (median) was higher in Japanese subjects than in non-Japanese subjects. As for baseline visual function, both mean and median values of FST (mean for both eyes, white light) were lower in the Japanese subjects than in the non-Japanese population, showing the higher light sensitivity in Japanese subjects. The mean and median values of visual acuity (mean for both eyes, Lange scale) were higher in the Japanese subjects than in the non-Japanese population, showing a tendency toward lower visual acuity in the Japanese subjects. The mean and median values of visual field were lower in the Japanese subjects than in the non-Japanese population for all indices evaluated, showing a tendency toward narrower visual field in the Japanese subjects.

The observed difference in the baseline visual function between the Japanese subjects and the non-Japanese population was attributed to the fact that the visual function in 2 Japanese subjects ([redacted] and [redacted]) substantially differed from that in the other 2 Japanese subjects ([redacted] and [redacted]) and the non-Japanese population.

Table 38. Baseline characteristics of patients (Study A11301, FAS; Study 301, mITT population)

Patient characteristics			Study A11301 (n = 4)	Study 301
Age		Mean ± SD	31.3 ± 20.69	14.8 ± 10.8 (n = 29)
		Median (range)	33 (1[redacted], 4[redacted])	11 ([redacted], 4[redacted])
Sex		Male	1 (25.0%)	11 (37.9%) (n = 29)
		Female	3 (75.0%)	18 (62.1%) (n = 29)
FST (mean for both eyes; white light; unit, log10 [cd.s/m^2])		Mean ± SD	−2.599 ± 1.3681	−1.41 ± 0.46 (n = 28)
		Median (range)	−2.642 (−3.85, −1.26)	−1.45 (−2.20, −0.13)
Visual acuity (mean for both eyes; Lange scale; unit, LogMAR)		Mean ± SD	1.616 ± 0.4553	1.07 ± 0.33 (n = 29)
		Median (range)	1.604 (1.11, 2.15)	0.99 (0.52, 1.87)
Kinetic visual field (mean for both eyes, Goldmann perimeter, sum total degrees for the 24 meridians)	Target size: III4e	Mean ± SD	189.5 ± 268.78	365.6 ± 395.4 (n = 28)
		Median (range)	86.0 (0, 586)	206 (0, 1418)
	Target size: V4e	Mean ± SD	670.0 ± 638.91	892.0 ± 444.8 (n = 24)
		Median (range)	662.3 (38, 1318)	942 (159, 1689)
Static visual field (mean for both eyes; Humphrey automated perimeter; unit, dB)	Foveal sensitivity	Mean ± SD	7.880 ± 7.5034	22.75 ± 6.66 (n = 28)
		Median (range)	8.185 (0, 15.15)	24.3 (5.5, 32.0)
	Macula threshold	Mean ± SD	9.428 ± 8.1683	16.31 ± 5.92 (n = 28)
		Median (range)	9.528 (2.16, 16.50)	15.8 (1.9, 26.3)

Table 39. Baseline characteristics of individual patients (Study A11301)

		Study A11301			
		[redacted]	[redacted]	[redacted]	[redacted]
Age/sex		4[redacted]	1[redacted]	1[redacted]	4[redacted]
FST (mean for both eyes; white light; unit, log10 [cd.s/m^2])		−3.85	−1.26	−1.58	−3.71
Visual acuity (mean for both eyes; Lange scale; unit, LogMAR)		2.15	1.11	1.41	1.80
Kinetic visual field (mean for both eyes, Goldmann perimeter, sum total degrees for the 24 meridians)	Target size: III4e	0	119	586	53
	Target size: V4e	38	1318	1112	213
Static visual field (mean for both eyes; Humphrey automated perimeter; unit, dB)	Foveal sensitivity	0	13.37	15.15	3.00
	Macula threshold	2.56	16.50	16.50	2.16

Table 40 shows the results of each endpoint from baseline to Year 1 after the second-eye injection in the FAS of Study A11301 and in the mITT population of Study 301.

Table 40. Changes in each endpoint from baseline to Year 1 after the second-eye injection (Study A11301, FAS; Study 301, mITT population)

Endpoint			Study A11301 (n = 4)	Study 301
FST (mean for both eyes; white light; unit, log10 [cd.s/m^2])		Mean ± SD	−1.831 ± 1.4910	−2.34 ± 1.57 (n = 28)
		Median (range)	−1.613 (−3.54, −0.56)	−2.17 (−5.61, 0.30)
Visual acuity (mean for both eyes; Lange scale; unit, LogMAR)		Mean ± SD	−0.033 ± 0.1428	−0.15 ± 0.21 (n = 29)
		Median (range)	−0.075 (−0.15, 0.17)	−0.15 (−0.61, 0.37)
Kinetic visual field (mean for both eyes, Goldmann perimeter, sum total degrees for the 24 meridians)	Target size: III4e	Mean ± SD	427.8 ± 514.29	267.4 ± 276.2 (n = 28)
		Median (range)	354.0 (−11, 1014)	257 (−215, 820)
	Target size: V4e	Mean ± SD	200.5 ± 303.52	68.3 ± 152.9 (n = 11)
		Median (range)	86.5 (−18, 647)	23 (−146, 308)
Static visual field (mean for both eyes; Humphrey automated perimeter; unit, dB)	Foveal sensitivity	Mean ± SD	3.734 ± 4.9991	2.64 ± 10.09 (n = 28)
		Median (range)	3.295 (−1.29, 9.63)	4.5 (−24.0, 20.5)
	Macula threshold	Mean ± SD	0.790 ± 2.8837	6.88 ± 7.51 (n = 28)
		Median (range)	1.108 (−2.56, 3.50)	7.8 (−12.3, 18.9)

As shown below, there were no tendencies toward substantial difference between results in the FAS of Study A11301 and those in the mITT population of Study 301, although the results need to be cautiously interpreted because of the limited number of Japanese subjects.

- FST (mean for both eyes, white light): The change in FST from baseline to Year 1 after the second-eye injection was similar between the populations.

- Visual acuity (mean for both eyes, Lange scale): In Study A11301, the change in visual acuity from baseline to Year 1 after the second-eye injection was small in all 4 subjects throughout the study period, and the change in the subjects were within the range of the change observed in Study 301.
- Kinetic visual field (mean for both eyes; Goldmann visual field perimetry; target size, III4e and V4e): In 3 of 4 subjects in Study A11301, the change in kinetic visual field was within the range of the change observed in Study 301 for both target sizes. The remaining 1 subject ([redacted]) showed substantial improvement surpassing the range observed in Study 301 for both target sizes.
- Static visual field (mean for both eyes, Humphrey automated perimeter, foveal sensitivity, and macula threshold): The change in foveal sensitivity from baseline to Year 1 after the second-eye injection in all 4 subjects of Study A11301 was within the range of change observed in Study 301. Little change was observed in 2 subjects ([redacted] and [redacted]) who showed decreased foveal sensitivity at baseline, whereas the remaining 2 subjects ([redacted] and [redacted]) showed increased (improved) foveal sensitivity and the improved state was maintained for 1 year after the second-eye injection. For macula threshold, no clear change was observed during the period from baseline to Year 1 after the second-eye injection in individual subjects in Study A11301, with the change being within the range of change observed in Study 301 in all 4 subjects.

As described above, in the Japanese subjects of Study A11301, the mean change (range) in FST (mean for both eyes, white light) from baseline to Year 1 after the second-eye injection was −1.831 (−3.54 to −0.56) log10 (cd.s/m^2). In 2 of 4 subjects, FST decreased by ≥2 log10 (cd.s/m^2), which was greater than the clinically significant threshold (1 log10 [cd.s/m^2]) (*Lancet.* 2017;390:849-60), showing improvement in light sensitivity as in Study 301. Kinetic visual field, static visual field (macula threshold), and visual acuity as the secondary endpoints also tended to show improvement after Luxturna administration. In view of the results of Study 301 suggesting correlation between the MLMT score using both eyes and FST, Luxturna is expected to improve functional vision in Japanese patients as well.

PMDA's view:
Luxturna is expected to have a certain extent of efficacy, judging from the following findings: (1) In Study 301, a statistically significant difference was observed in the MLMT score using both eyes from baseline to Year 1 after the second-eye injection (at 1 year from baseline in the control group), the primary endpoint, and visual function assessed by FST tended to improve in the Luxturna group compared to the control group; and (2) in the long-term follow up of Study 301, the improved FST was maintained for a long period of time, i.e., until the most recent data cut-off date, and kinetic visual field, static visual field (macula threshold), and visual acuity also tended to show improvement, although there was little improvement in static visual field (foveal sensitivity), a pyramidal cell-mediated function.

Results of Study A11301 suggest the efficacy of Luxturna in Japanese patients as well. Because of the extremely limited number of Japanese patients investigated in the clinical study, the applicant should collect data on the efficacy of Luxturna in Japanese patients in the post-marketing setting.

7.R.3 Safety

7.R.3.1 Safety profile of Luxturna and its difference between Japanese and non-Japanese patients

The applicant's explanation about the safety of Luxturna:

Tables 41 to 44 show the summary of safety in Studies 301, A11301, 101, and 102.

Table 41. Summary of safety
(Study 301, safety analysis population, period from the first-eye injection to Year 1 after the second-eye injection in the Luxturna group [1 year from baseline in the control group])

	Luxturna (N = 20)	Control (N = 9)
Subjects with any adverse event	20 (100)	9 (100)
Adverse events for which a causal relationship to Luxturna could not be ruled out	0	-
Adverse events related to injection procedure	13 (65.0)	-
Serious adverse events	2 (10.0)	0
Highly severe adverse events	3 (15.0)	0
Adverse events leading to study discontinuation	0	0
Adverse events leading to death	0	0

n (%)

Table 42. Summary of safety (Study A11301, safety analysis population, data cut-off* on [redacted], 20[redacted])

	Luxturna (N = 4)
Subjects with any adverse event	4 (100)
Adverse events for which a causal relationship to Luxturna could not be ruled out	0
Adverse events related to injection procedures	2 (50.0)
Adverse events related to perioperative corticoid administration	4 (100)
Serious adverse events	1 (25.0)
Highly severe adverse events	0
Adverse events leading to study discontinuation	0
Adverse events leading to death	0

n (%)
* From the first dose of Luxturna to the data cut-off date at 1 year after injection in the second-treated eye of the last subject

Table 43. Summary of safety
(Studies 101 and 102, safety analysis population, data cut-off* on [redacted], 20[redacted])

	Study 101			Study 102
	Low-dose cohort (N = 3)	Medium-dose cohort (N = 6)	High-dose cohort (N = 3)	(N = 11)
Subjects with any adverse event	3 (100)	6 (100)	3 (100)	11 (100)
Adverse events for which a causal relationship to Luxturna could not be ruled out	0	0	0	0
Adverse events related to injection procedure	3 (100)	5 (83.3)	2 (66.7)	7 (63.6)
Serious adverse events	1 (33.3)	0	0	1 (9.1)
Highly severe adverse events	0	0	0	1 (9.1)
Adverse events leading to study discontinuation	0	0	0	0
Adverse events leading to death	0	0	0	0

n (%)
* The safety data from Study 101 include those reported from the day of injection of Luxturna to the day of participation in Study 102 or to the data cut-off date. The safety data from Study 102 include those reported from the day of injection of Luxturna in the contralateral eye untreated in Study 101 to the data cut-off date.

Table 44. Summary of safety
(Studies 101/102 and 301, safety analysis population, long-term follow up [data cut-off on [redacted], 20[redacted]][*1])

	Study 101/102	Study 301	
		Luxturna	Control/Luxturna
	(N = 12)	(N = 20)	(N = 9)
Subjects with any adverse event	12 (100)	20 (100)	9 (100)
Adverse events for which a causal relationship to Luxturna could not be ruled out	0	0	3 (33.3)
Ocular adverse events[*2]	11 (91.7)	12 (60.0)	7 (77.8)
Adverse events related to injection procedure	11 (91.7)	13 (65.0)	6 (66.7)
Serious adverse events	5 (41.7)	6 (30.0)	2 (22.2)
Adverse events leading to study discontinuation	0	0	0
Adverse events leading to death	0	0	0

n (%)
*1 The safety data from Study 101/102 include those reported from the day of injection of Luxturna in Study 101 to the data cut-off on [redacted], 20[redacted]. The safety data from Study 301 include those reported from the day of the first-eye injection of Luxturna to the data cut-off date.
*2 Adverse events coded to SOC "Eye disorders" or those containing the term "intraocular pressure (IOP)" or "eye" in the event names reported by the physician.

Table 45 shows the incidence of adverse events related to the injection procedure (those reported in ≥2 subjects in clinical studies).

Table 45. Incidence of adverse events related to injection procedure in ≥2 subjects
(safety analysis population)

	Study 101[*1] (N = 12)	Study 102[*1] (N = 11)	Study 301[*2] (N = 29)	Study A11301[*2] (N = 4)	Total[*3] (N = 45)
Any adverse event related to injection procedure	10 (83.3)	7 (63.6)	19 (65.5)	2 (50.0)	31 (68.9)
Conjunctival hyperaemia	8 (66.7)	0	1 (3.4)	0	9 (20.0)
Cataract	0	2 (18.2)	4 (13.8)	0	6 (13.3)
Intraocular pressure increased	0	2 (18.2)	4 (13.8)	0	6 (13.3)
Eye pain	0	1 (9.1)	1 (3.4)	2 (50.0)	4 (8.9)
Retinal tear	1 (8.3)	0	3 (10.3)	0	4 (8.9)
Nausea	0	0	3 (10.3)	0	3 (6.7)
Eye inflammation	0	1 (9.1)	2 (6.9)	0	3 (6.7)
Macular hole	1 (8.3)	0	2 (6.9)	0	3 (6.7)
Headache	0	1 (9.1)	2 (6.9)	0	3 (6.7)
Dellen	0	3 (27.3)	0	0	3 (6.7)
Vomiting	0	0	2 (6.9)	0	2 (4.4)
Eye irritation	0	1 (9.1)	1 (3.4)	0	2 (4.4)
Endotracheal intubation complication	1 (8.3)	0	1 (3.4)	0	2 (4.4)

MedDRA Version 23.0 in Studies 101, 102, and 301. MedDRA Version 25.0 in Study A11301
n (%)
*1 Events that occurred from the injection of Luxturna to Year 1 after the injection in each study
*2 Events that occurred during the period from the first-eye injection to Year 1 after the second-eye injection
*3 Any of 12 subjects participating in Study 101 and/or Study 102 who had the same adverse event in either of the studies was counted as 1 subject.

The safety of Luxturna in Japanese patients was evaluated by comparing the safety data in the safety analysis population (n = 29) in the foreign Study 301 from the first-eye injection to Year 1 after the second-eye injection, with those in the safety analysis population (n = 4) in the Japanese Study A11301 during the same period.

Adverse events with a ≥30% higher incidence in Study A11301 than in Study 301 were white blood cell count increased in 4 subjects (4 subjects [100%] in Study A11301 vs. 0 subjects [0%] in Study 301), constipation (2 subjects [50%] in Study A11301 vs. 1 subject [3.4%] in Study 301), and eye pain (2 subjects [50%] in Study A11301 vs. 2 subjects [6.9%] in Study 301). All of the adverse events in Study A11301 were mild and resolved without intervention. White blood cell count increased occurred

1 to 8 days after Luxturna administration and was assessed as related to perioperative corticosteroid use. Constipation was assessed as related to perioperative corticosteroid use, and eye pain was assessed as related to the injection procedure.

Adverse events reported only in Study A11301 were white blood cell count increased, abdominal pain, dry eye, dry skin, adnexal torsion (the event name was changed to ovarian cyst torsion at or after 1 year after Luxturna administration), and myalgia. All of the adverse events, except white blood cell count increased, were assessed as unrelated to the injection procedure or perioperative corticosteroid use. Each of these adverse events was reported in only 1 subject. In Study 301, leukocytosis was reported in 11 subjects (37.9%).

Thus, there were no new safety concerns specific to Japanese subjects, showing no significant difference in the safety profile between Study A11301 and Study 301, although the interpretation of the results has limitations because the number of subjects included in Study A11301 is as extremely small as 4.

PMDA's view:
Currently available evidence on the safety of Luxturna, albeit extremely limited, suggests the necessity of particular caution against ocular adverse events related to the injection procedure which were frequently reported in the clinical studies of Luxturna. However, there were no serious safety concerns about adverse events assessed as related to Luxturna. The safety of Luxturna is acceptable on the premise that appropriate measures, such as monitoring and management of adverse events, are taken by physicians and surgeons with sufficient knowledge and experience in subretinal surgery. Only 4 Japanese patients have been treated with Luxturna and have not been followed up for a sufficient length of period. Nevertheless, there have been no events of particular concern in Japanese patients.

The following subsections show the results of the analyses of important events reported in clinical studies or in the foreign post-marketing data.

7.R.3.2 Ocular adverse events

The applicant's explanation about ocular adverse events after Luxturna administration:
Ocular adverse events (defined as events coded to system organ class [SOC] "Eye disorders" and those containing the term "intraocular pressure [IOP]" or "eye" in event names reported by the physician) which were specified as noteworthy safety endpoints were reported in 11 subjects (91.7%) in Study 101/102 (including the long-term follow-up period), in 19 subjects (65.5%) in Study 301 (including the long-term follow-up period), and in 4 subjects (100%) in Study A11301 (at Year 1 after the second-eye injection of Luxturna).

The most common ocular adverse events (those with an incidence of ≥15% in each study) were conjunctival hyperaemia (8 subjects, 66.7%), cataract (5 subjects, 41.7%), dellen (3 subjects, 25.0%), intraocular pressure increased (3 subjects, 25.0%), eye irritation (2 subjects, 16.7%), and eye pain (2 subjects, 16.7%) in Study 101/102; cataract (8 subjects, 27.6%) and intraocular pressure increased (5 subjects, 17.2%) in study 301; and eye pain (2 subjects, 50.0%), dry eye (1 subject, 25.0%), and

intraocular pressure increased (1 subject, 25.0%) in Study A11301. Except retinal deposits reported in Study 101 and assessed as related to Luxturna, most of the ocular adverse events were assessed as related to the injection procedure, and resolved with or without intervention.

Conjunctival hyperaemia, one of the most common ocular adverse events in Study 101/102, included findings such as irritation of eye surface, suture reaction, and suture irritation. They were caused by a slow-resorbing suture used at the incision site in some of the subjects. Sensation of foreign body associated with conjunctival hyperaemia was manageable with the use of topical steroids and antibiotics as the standard post-operative treatments for subretinal surgery.

Table 46 shows the incidence of ocular adverse events during the long-term follow-up. These ocular adverse events were deemed as significant events from the perspective of potential to arise from the injection procedure and to induce severe visual impairment.

Table 46. Incidence of ocular adverse events deemed significant (safety analysis population)

	Study 101/102[*1] (N = 12)	Study 301[*2] (N = 29)	Study A11301[*3] (N = 4)	Total (N = 45)
Cataract	5 (41.7)	8 (27.6)	0	13 (28.9)
Intraocular pressure increased	3 (25.0)	5 (17.2)	1 (25.0)	9 (20.0)
Macular disease	3 (25.0)	4 (13.8)	0	7 (15.6)
Retinal tear	1 (8.3)	3 (10.3)	0	4 (8.9)
Endophthalmitis or eye infection intraocular associated with injection procedure	1 (8.3)	3 (10.3)	0	4 (8.9)
Retinal detachment	0	2 (6.9)	0	2 (4.4)

n (%)
*1 Events that occurred from the first injection of Luxturna to the data cut-off on [redacted], 20[redacted]
*2 Events that occurred from the first injection of Luxturna to the data cut-off on [redacted], 20[redacted]
*3 Events that occurred from the first injection of Luxturna to the data cut-off on [redacted], 20[redacted]

- Cataract

Cataract occurred in 5 subjects (7 events) in Study 101/102. No subjects had cataract at baseline. All events were non-serious and mild or moderate in severity. Cataract in 4 subjects was assessed as related to the injection procedure. In 1 subject, cataract (mild) was persisting at the data cut-off in [redacted] 20[redacted], but other events of cataract resolved without sequelae. Most events of cataract occurred ≥1 year after Luxturna administration. Subjects experiencing cataract ranged from 17 to 44 years of age at the time of the first-eye injection of Luxturna (1 subject <18 years of age and 4 subjects ≥18 years of age).

In Study 301, cataract occurred in 8 subjects (14 events). Of these, 2 subjects had cataract in both eyes at baseline. All were non-serious and mild or moderate in severity. All of the events were assessed as unrelated to Luxturna. All but 1 event were assessed as related to the injection procedure. Most of them occurred ≥1 year after Luxturna administration. Ten of 14 events were persisting at the data cut-off in [redacted] 20[redacted], while other events resolved without sequelae or were resolving. Subjects experiencing cataract ranged from 5 to 34 years of age at the time of the first-eye injection of Luxturna (3 subjects age of <18 years of age and 5 subjects ≥18 years of age).

Cataract was not reported in Study A11301.

According to published literature, the incidence of cataract reported as a complication of vitreous surgery was 31.7% (*Ophthalmol Ther*. 2022;11:2225-42), 8% to 21% (*Eur J Ophthalmol.* 2021;31:1367-74), 79.3% (*Am J Ophthalmol.* 2005;139:831-6), and 80% (*Curr Opin Ophthalmol.* 2020;31:167-73).

- Intraocular pressure increased

In Study 101/102, intraocular pressure increased occurred in 3 subjects (7 events). One event in 1 subject was considered to be a serious adverse event. This event was attributed to depo-corticosteroid administered to treat inflammation associated with endophthalmitis after vitrectomy and assessed as unrelated to Luxturna or the injection procedure. In this subject, optic atrophy (nonserious, moderate) occurred due to intraocular pressure increased, but the intraocular pressure returned to the normal level after glaucoma filtration surgery (trabeculectomy). Other 6 events were non-serious and mild or moderate in severity. All of the 6 events of intraocular pressure increased were assessed as unrelated to Luxturna. While 2 of the events were assessed as related to the injection procedure, the remaining 4 events were considered unrelated. Of the 7 events, 3 occurred within 1 month after subretinal administration of Luxturna. All events resolved.

In Study 301, intraocular pressure increased occurred in 5 subjects (7 events). All were non-serious and mild in severity. Of the 7 events, 6 occurred within 1 month after Luxturna administration. One event in 1 subject was assessed as unrelated to Luxturna or the injection procedure, while all other events were assessed as unrelated to Luxturna but related to the injection procedure. All events resolved without intervention or by treatment with drugs etc.

In Study A11301, intraocular pressure increased occurred in 1 subject (1 event). It was mild and assessed as unrelated to Luxturna or the injection procedure. The event occurred within 1 month after Luxturna administration and resolved 7 days after administration of an ophthalmic drug.

According to published literature, the incidence of intraocular pressure increased reported as a complication of vitreous surgery was 12.3% (defined as an increase of >30 mmHg, *Asia Pac J Ophthalmol (Phila).* 2019;8:36-42) and 20% (defined as an increase of >20 mmHg, *J Ophthalmol.* 2021;doi:10.1155/2021/5588479).

- Macular disease

Macular disease occurred in 3 subjects (3 events) in Study 101/102, in 4 subjects (8 events) in Study 301, and in none in Study A11301. Except serious retinal fovea disorder which occurred in the right eye of 1 subject in Study 301, all events were non-serious and mild or moderate in severity. All events were assessed as unrelated to Luxturna but related to the injection procedure. Of the 11 events, 7 occurred within 1 month after subretinal administration. Six events resolved without intervention or by treatment with drugs etc. According to published literature, the incidence of macular disease reported as a complication of vitreous surgery was 9% (*Retina.* 2012;32:1350-5), 13% (*Retina.* 2008;28:744-8), and 29.3% (*J Ophthalmol.* 2021;doi:10.1155/2021/5588479).

• Retinal tear and retinal detachment

Retinal tear occurred in 1 subject (1 event) in Study 101/102 and in 3 subjects (3 events) in Study 301. All were non-serious and mild or moderate in severity. All events were assessed as unrelated to Luxturna but related to the injection procedure. All events resolved without sequelae after treatment with laser photocoagulation etc. These events occurred within 2 weeks after subretinal administration.

Retinal detachment occurred in 2 subjects (2 events) in Study 301. One event was reported as a serious adverse event and resolved after vitreous surgery or other treatments, but the outcome of the event was "resolved with sequelae." The event in the other subject was non-serious and resolved after treatment with laser photocoagulation. Both events were assessed as unrelated to Luxturna but related to the injection procedures. The events occurred 4 to 5 years after subretinal administration. In Study A11301, neither retinal tear nor retinal detachment occurred.

According to published literature, the incidence of retinal tear reported as a complication of vitreous surgery was 5% (Vitrectomy. (http://www.oculist.net/downaton502/prof/ebook/duanes/pages/v6/v6c056.html#com [last accessed on May 9, 2022]), 3.1% to 6.4% (*Am J Ophthalmol.* 2007;143:155-6), 15% (*Ophthalmology.* 2010;117:1825-30), 2.2% (*Am J Ophthalmol.* 2008;146:193-7), 3.8% to 25% (*PLoS One.* 2022;17:e0272333), and the incidence of retinal detachment was 1.54% (*Ophthalmol Ther.* 2022;11:2225-42), 2% (*Ophthalmology.* 2010;117:1825-30), and 5.8% (*Asia Pac J Ophthalmol (Phila).* 2019;8:36-42).

• Endophthalmitis or intraocular infection related to injection procedure

Data on adverse events reported as endophthalmitis or intraocular infection related to the injection procedure were analyzed. Eye inflammation occurred in 1 subject (1 event) in Study 101/102, in 3 subjects (7 events) in Study 301, and in none in Study A11301. All were non-serious and mild or moderate in severity. All the evens were assessed as unrelated to Luxturna. Except 1 event in 1 subject in Study 301, all were assessed as related to the injection procedure. One subject ([redacted]) in Study 101/102 had eye inflammation 11 days after the second-eye injection (right eye), and underwent treatment with antibiotics and sub-Tenon's injection of depo-corticosteroid. Cultures of the vitreous fluid were positive for *Staphylococcus epidermidis*. This event was resolved with medical treatment, while the subject had optic atrophy due to intraocular pressure increased caused by depo-corticosteroid injection and cataract caused by depo-corticosteroid injection and filtration surgery (trabeculectomy) to treat intraocular pressure increased. Optic atrophy was persisting but cataract resolved without sequelae. All other events reported in Study 301 also resolved without sequelae. All of these events occurred within 2 weeks after subretinal administration. In Study 101/102, the clinical study protocol was revised following these events. The revisions included changes to procedures for the preparation of Luxturna to minimize the risk of contamination as well as retraining on the surgical procedures of vitrectomy and on the preparation of Luxturna. In Studies 301 and A11301 conducted after the revision of the protocol, there have been no events containing the term endophthalmitis in the event name reported or preferred term (PT).

According to the published literature, the incidence of endophthalmitis reported as a complication of vitreous surgery was 0.03% to 0.07% (*Postoperative endophthalmitis*. (http://emedicine.medscape.com/article/1201260-overview [last accessed on February 20, 2017]) and 0.18% (*Ophthalmol Ther*. 2022;11:2225-42). In the clinical studies of Luxturna, the definition of endophthalmitis or intraocular infection includes broad PTs, and the event with the same definition as "Endophthalmitis" used in the published reports was observed only in 1 subject, suggesting that the incidence of endophthalmitis is not significantly different from that in the published reports.

Below is shown the incidence of "vision loss due to progressive chorioretinal atrophy," an important ocular adverse event newly defined based on events reported in the foreign post-marketing data, albeit not reported in clinical studies.

- Vision loss due to progressive chorioretinal atrophy

During the period from the launch on the foreign markets to [redacted], 20[redacted], events related to chorioretinal atrophy were reported for 106 eyes of 68 patients[34)] with the reporting ratio of 0.12, calculated from the cumulative number of patients treated with Luxturna (886 eyes of 456 patients) in the post-marketing setting. Their relationship to visual impairment-related events was investigated in 68 patients who had chorioretinal atrophy-related events. Results showed visual impairment-related events in 11 patients and suggested the possibility of vision loss due to progressive chorioretinal atrophy in 2 of them.

Thus, the type and frequency of ocular adverse events reported in the clinical studies of Luxturna were largely consistent with those of postoperative complications caused by commonly practiced vitreous surgery or subretinal injection procedures, suggesting that these adverse events are manageable by appropriate interventional procedures. The applicant will evaluate the incidence of ocular adverse events continuously in the post-marketing setting, including the risk of "vision loss due to progressive chorioretinal atrophy" newly reported in the foreign post-marketing data.

PMDA's view:

Most of ocular adverse events reported in the clinical studies or the foreign post-marketing data occurred shortly after Luxturna administration and resolved without sequelae, whereas there were some events which led to permanent vision loss or occurred several years after Luxturna administration, warranting caution in administering Luxturna and requiring close follow-up monitoring after Luxturna administration. The information on the incidences of ocular adverse events after Luxturna administration should be included in the package insert to raise awareness. In addition, the applicant should collect pot-marketing safety information and should promptly provide any available information to healthcare professionals.

34) Events coded to the following PTs in MedDRA PT version 25.0 were collected: "Chorioretinal disorder," "Injection site atrophy," "Myopic choroidal degeneration," "Retinal degeneration," "Retinal depigmentation," "Retinal dystrophy," or "Retinal pigment epitheliopathy."

7.R.3.3 Tumorigenicity

The applicant's explanation about the tumorigenicity of Luxturna:

Tumorigenicity-related events were reported in 4 subjects (6 events) in Study 101/102 (adenomatous polyposis coli, haemangioma, meningioma benign, oral papilloma, pyogenic granuloma, and gastric polyps) and in 3 subjects (3 events) in Study 301 (oral fibroma, acute myeloid leukaemia, and conjunctival cyst). In Study A11301, 1 subject had adnexal torsion, but the event name was changed to ovarian cyst torsion after the data cut-off on [redacted], 20[redacted], and considered to be a tumorigenicity-related event. This event was reported as a serious adverse event but resolved with interventions. While acute myeloid leukaemia in 1 subject in Study 301 was severe, other events reported in Study 301 were mild or moderate in severity. Adenomatous polyposis coli in Study 101/102, acute myeloid leukaemia in Study 301, and ovarian cyst torsion in Study A11301 were reported as serious events. Their outcome at the data cut-off on [redacted], 20[redacted] were "resolved" for adenomatous polyposis coli and ovarian cyst torsion, and "death" for acute myeloid leukaemia. All of the events were assessed as unrelated to Luxturna. Pyogenic granuloma occurred approximately 10 months after Luxturna administration but the time to onset was unknown for haemangioma and meningioma benign in Study 101/102. Conjunctival cyst occurred approximately 3 months after administration and oral fibroma approximately 10 months after administration in Study 301. Ovarian cyst torsion occurred approximately 10 months after administration in Study A11301. Other events were reported sporadically from approximately 3 years after Luxturna administration onward during the long-term follow-up.

According to the foreign post-marketing data, tumorigenicity-related events were reported in 2 patients (pyogenic granuloma, conjunctival cyst) before the data cut-off on [redacted], 20[redacted]. Both events occurred within 3 months after Luxturna administration and were non-serious. The outcome was "resolved" for both events.

As described above, only few events related to tumorigenicity were reported in the clinical studies or the foreign post-marketing data, and all of the events were assessed as unrelated to Luxturna. However, since the possible causal relationship between Luxturna and tumorigenicity has not been fully elucidated, the applicant will collect relevant information in the post-marketing setting to consider the necessity of cautionary advice

PMDA's view:

There were few events of malignancies in the clinical studies, etc., of Luxturna, nor has any ocular tumor been reported. However, because of the limited number of patients treated with Luxturna, the applicant should continue to collect information on the incidences of tumorigenicity-related events in the post-marketing setting.

7.R.4 Clinical positioning of Luxturna

The applicant's explanation about the clinical positioning of Luxturna in the treatment of biallelic *RPE65* mutation-associated IRD:

Patients with biallelic *RPE65* mutation-associated IRD are devoid of the activity of RPE65 protein, one of the enzymes involved in the biochemistry of light absorption by photoreceptor cells of the

retinal membrane. Defect of the enzyme activity causes accumulation of cytotoxic substances, resulting in the degeneration/necrosis of other retinal cells. In these patients, rod cells mainly responsible for vision in peripheral and dark fields are impaired, causing progressive marked reduction in visual acuity, afferent visual field constriction, night blindness, and nystagmus, eventually resulting in blindness in most cases. Night blindness is a symptom characteristic to the disease and, in an advanced state, interferes with vision-related activities of daily life even under the day-light.

The currently available treatment in Japan is administration of Adaptinol tablets 5 mg (non-proprietary name, helenien), which is approved for the indication of "temporary improvement in visual field and dark adaptation in retinitis pigmentosa," but its efficacy is limited and there is no established treatment for biallelic *RPE65* mutation-associated IRD.

The applicant considers that Luxturna provides a novel treatment option for patients with biallelic *RPE65* mutation-associated IRD because the results of Studies 101, 102, 301, and A11301 have demonstrated the efficacy and safety of Luxturna in patients with this disease [see Sections 7.R.2 and 7.R.3].

PMDA accepted the above explanation of the applicant. The appropriateness of "Indication or Performance" will be discussed in Section "7.R.5.1 Appropriateness of the proposed indication of Luxturna i.e., biallelic *RPE65* mutation-associated inherited retinal dystrophy."

7.R.5 Indication or performance

The proposed "Indication or Performance" was "Biallelic *RPE65* mutation-associated inherited retinal dystrophy." "Precautions Concerning Indication or Performance" was proposed as follows:

(1) Luxturna should be administered to patients with biallelic *RPE65* mutation confirmed by genetic test.
(2) Luxturna should be administered to patients who have sufficient viable retinal cells.

PMDA concluded that the proposed descriptions of "Indication or Performance" are acceptable, based on the reviews addressed in Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4. Clinical positioning of Luxturna," and on the reviews in the subsections below. Further, PMDA concluded that the "Precautions Concerning Indication or Performance" section should be specified as shown below:

Indication or Performance

Biallelic *RPE65* mutation-associated inherited retinal dystrophy

Precautions Concerning Indication or Performance (Underline denotes addition.)

(1) Luxturna should be administered to patients with biallelic *RPE65* mutation confirmed by genetic test.
(2) Luxturna should be administered to patients who <u>are confirmed to</u> have sufficient viable retinal cells <u>by an appropriate test</u>.

7.R.5.1 Appropriateness of the proposed indication of Luxturna i.e., biallelic *RPE65* mutation-associated inherited retinal dystrophy

Studies 101, 102, and 301 included patients diagnosed with biallelic *RPE65* mutation-associated LCA. In Study A11301 involving patients with biallelic *RPE65* mutation-associated IRD, 4 subjects (2 patients with RP and 2 patients with LCA) were enrolled. In contrast to the 2 patients with LCA, the 2 patients with RP did not show clinically significant improvement of >1 in FST [see Section 7.1.2.1, Table 33].

In the clinical studies, the efficacy and safety of Luxturna were investigated mainly in patients with LCA, with only limited information available on the efficacy and safety of Luxturna in patients with RP. PMDA asked the applicant to explain the appropriateness of specifying the "Indication or Performance" as patients with "biallelic *RPE65* mutation-associated inherited retinal dystrophy" including patients with RP.

The applicant's response:

For reasons described in (a) and (b) below, it is appropriate to specify the "Indication or Performance" of Luxturna as patients with "biallelic *RPE65* mutation-associated inherited retinal dystrophy" including patients with RP.

(a) Clinical diagnostic term

Patients with biallelic *RPE65* mutation-associated IRD are generally diagnosed with either LCA or RP, but the definitions of both terms are not clearly distinguished. As a result, a single patient with biallelic *RPE65* mutation-associated IRD is sometimes diagnosed with different disease names, including LCA and RP. In a retrospective study (Natural History Study) on the spontaneous course of patients with biallelic *RPE65* mutation-associated IRD (*Am J Ophthalmol.* 2019;199:58-70), 70 patients were initially diagnosed with as many as 76 disease names which were classified into 21 types of diseases; some patients were diagnosed with multiple disease names. There were patients for whom the disease name was changed based on information such as the genetic test results that became available after the initial diagnosis. There were also patients diagnosed with both LCA and RP. There is an increasing need to make a diagnosis of IRD based on the causative gene, as diagnosing IRD based on clinical symptoms can be inaccurate (e.g., *Int J Mol Sci.* 2021;22:7207).

LCA is a disease related to RP, often showing similar clinical symptoms. The definition of each disease is not clearly differentiated. The cause of biallelic *RPE65* mutation-associated IRD is impairment of visual cycle caused by the lack of RPE65 protein regardless of diagnosis name. Accordingly, patients eligible for treatment with Luxturna should be selected based not on the clinical diagnosis name but on the causative gene.

(b) Efficacy of Luxturna in patients with IRD other than LCA

In Study 301, "patients with a diagnosis of LCA due to biallelic *RPE65* mutation based on confirmation of the molecular/genetic diagnosis by a clinical laboratory improvement amendments (CLIA)-certified laboratory" was one of the inclusion criteria, but RP or other diagnosis names related to IRD were not specified in the exclusion criteria. In this study, symptoms characteristic to RP were entered in the clinical record of 1 subject ([redacted]), and another subject ([redacted]) had been diagnosed

with RP by the previous attending doctor, albeit reference information. In both subjects, the mean change in the MLMT score using both eyes from baseline to Year 1 after the second-eye injection was 1, a value indicating clinically significant improvement.

According to the foreign post-marketing data, Luxturna was administered to patients with biallelic *RPE65* mutation-associated RP, who showed improvement in FST, visual acuity, and visual field at 3 months after Luxturna administration, with favorable tolerability (*Yonsei Med J.* 2022;63:701-5).

Thus, the information obtained from clinical studies of Luxturna and the post-marketing data suggest the efficacy of Luxturna in patients with a diagnosis of RP. The efficacy of Luxturna in patients with IRD other than LCA is promising.

PMDA's view:
The following explanation of the applicant is understandable: The diagnosis names for patients with biallelic *RPE65* mutation-associated IRD vary, and their definitions are not clearly differentiated. Therefore, given the mechanism of action of Luxturna, patients eligible for treatment with Luxturna should be selected based not on the clinical diagnosis name but on the causative gene. However, because of the extremely limited experience with the use of Luxturna in patients with IRD who have other diagnosis name than LCA, the applicant should continue to collect information on the efficacy and safety of Luxturna in the post-marketing setting.

7.R.5.2 Method for confirming that patients have sufficient viable retinal cells

The "Precautions Concerning Indication or Performance" section for Luxturna specifies that Luxturna should be administered to patients with sufficient viable retinal cells. PMDA asked the applicant to explain the necessity of providing healthcare professionals in clinical practice with the information on testing whether patients have sufficient viable retinal cells.

The applicant's response:
In Studies 301 and A11301, relevant criteria were clearly defined [see Table 25 in Section 7.1.1.3 and Table 31 in Section 7.1.2.1] for standardization of the subject population, and the structure of the retina (by optical coherence tomography [OCT] and funduscopy) and retinal function (visual function) were tested to determine the presence of a sufficient number of viable retinal cells.

It is inappropriate, however, to establish and uniformly apply definite criteria because (1) appropriate tests may differ from patient to patient in clinical practice (for example, OCT may not be easily performed if patients are non-cooperative or have severe nystagmus); or (2) in the future, superior testing methods may become available thanks to the rapid progress in the test technology. Instead, the best option will be that ophthalmologists with sufficient professional knowledge of retinal disorders, based on the overall clinical assessment of individual patients, determine the presence of a sufficient number of viable retinal cells so as to decide whether they can be benefited from treatment with Luxturna.

Luxturna gene therapy is performed at medical institutions with multiple physicians and surgeons who have sufficient professional knowledge and experience on the diagnosis and treatment of retinal diseases including IRD and are well-informed of necessary information on the proper use of Luxturna. This allows the comprehensive assessment of eligibility of individual patients for treatment with Luxturna, after the determination of presence of a sufficient number of viable retinal cells according to the method best suited to each patient.

Thus, there is no need to describe the diagnostic methods employed in Studies 301 or A11301 in the package insert. The inclusion/exclusion criteria used in Studies 301 and A11301, which served as the assessment criteria, will be included in the information material.

PMDA's view:
The above explanation of the applicant is generally understandable. However, the criteria used to determine the presence of a sufficient number of viable retinal cells for enrolling patients in Studies 301 and A11301 provide important information for identifying the eligibility of patients with IRD for treatment with Luxturna. Therefore, the criteria used for enrolling subjects with sufficient viable retinal cells in Studies 301 and A11301 should be addressed in the "Clinical Studies" section of the package insert to provide information. In addition, the presence of a sufficient number of viable retinal cells should be determined based on the test suited to each patient. This information should therefore be addressed in the "Precautions Concerning Indication or Performance" section.

7.R.5.3 Use in children aged <3 years

The applicant's explanation about the use of Luxturna in children aged <3 years:
Patients aged <3 years were excluded from the clinical studies of Luxturna because of the difficulty in performing the injection procedure in the patient population. However, thanks to the recent advance in the equipment and techniques for retinal surgery in children, the risk of the injection procedure is no longer likely to increase in patients of this age group.

According to the foreign post-marketing data (until [redacted], 20[redacted]), the use of Luxturna was reported in 2 children aged <3 years (2 years of age and 22 months of age). In the patient aged 2 years, febrile convulsions occurred at 3.5 and 7 months after the second-eye injection of Luxturna, but a causal relationship to Luxturna or the injection procedure was ruled out for both events. The patient aged 22 months had retinal tear (unrelated to Luxturna but related to the injection procedure) after injection in the right eye and vitreous opacities and retinal deposits (related to Luxturna and unrelated to the injection procedure) after injection in the left eye. All were non-serious. Retinal tear resolved with laser photocoagulation, and vitreous opacities and retinal deposits resolved without clinical intervention. While Luxturna may be diluted and eliminated through the proliferation of retinal cells, the retinal tissue is still in the process of development until at least 12 months after birth (*Exp Eye Res.* 2008;87:415-26). In addition, there is only limited information on the use of Luxturna in children aged <3 years. Based on the above findings, "4. Use in Pregnant, Parturient, or Breast-feeding Women or in Children" section will include the cautionary statement that "(3) No clinical studies have been conducted involving underweight newborns, neonates, suckling babies, or infants aged <3 years."

Further, the applicant will collect information on the use of Luxturna in children aged <3 years in the post-marketing surveillance or by other means.

PMDA's view:
Although no clinical studies were conducted to investigate the use of Luxturna in children aged <3 years, it is acceptable to treat children aged <3 years with Luxturna on the premise that the package insert includes the cautionary statement that no clinical study has been conducted involving patients of this age group and that information on the safety and efficacy of Luxturna is collected in the post-marketing surveillance, because (1) there are foreign post-marketing reports on the use of Luxturna in patients of this age group; and (2) it may be considered appropriate to administer Luxturna at an early stage of the disease when there still remain sufficient viable retinal cells before the progression of retinal disorder due to biallelic *RPE65* mutation. In addition, the following information should be provided in the form of the package insert, etc.: (i) the retinal tissue is still in the process of development until at least 12 months after birth; and (ii) Luxturna may be diluted and eliminated through the proliferation of retinal cells.

7.R.5.4 Necessity of checking for anti-AAV2 antibody titer before Luxturna administration

PMDA asked the applicant to explain whether it is necessary to check for anti-AAV2 antibody titer before Luxturna administration.

The applicant's response:
It is unnecessary to check for anti-AAV2 antibody titer before Luxturna administration, for reasons described in (a) to (d) below:

(a) The efficacy of Luxturna by presence or absence[35)] of anti-AAV2 antibody at baseline (at injection baseline in the control/Luxturna group) assessed using data from Study 301. In the mITT population of Study 301, the change (mean ± SD) in the MLMT score using both eyes from baseline (from injection baseline in the control/Luxturna group) to Year 1 after the second-eye injection was 2.2 ± 0.9 in the antibody-negative subgroup (n = 15) and 1.6 ± 1.4 in the antibody-positive subgroup (n = 14), showing a greater improvement in the antibody-negative subgroup than in the antibody-positive subgroup. Results of analyses by treatment group showed that the change in the MLMT score was 2.4 ± 1.0 in the antibody-negative subgroup (n = 10) and 1.3 ± 0.8 in the antibody-positive subgroup (n = 10) in the Luxturna group; and 1.8 ± 0.8 in antibody-negative subgroup (n = 5) and 2.5 ± 2.4 in the antibody-positive subgroup (n = 4) in the control/Luxturna group. Thus, a greater improvement in the MLMT score was observed in the antibody-negative subgroup than in the antibody-positive subgroup in the Luxturna group, but in the antibody-positive subgroup than in the antibody-negative subgroup in the control/Luxturna group, showing no consistent results. In addition, in the anti-AAV2 antibody-positive subgroup, no clear correlation was observed between baseline anti-AAV2 antibody titer and change in the MLMT score.

[35)] Subjects with baseline anti-AAV2 antibody titer below quantification limit (BQL, 1.55 μg/mL) were defined as antibody-negative, and otherwise as antibody-positive.

(b) The safety of Luxturna by presence or absence of anti-AAV2 antibody at baseline (at injection baseline in the control/Luxturna group) was assessed based on the incidence of adverse events from the first-eye injection of Luxturna to Year 1 after the second-eye injection in the safety analysis population of Study 301. The adverse events with an incidence of ≥30% were nasopharyngitis, headache, and oropharyngeal pain (40.0% each [6 of 15 subjects]), and leukocytosis (33.3% [5 of 15 subjects]) in the antibody-negative subgroup (n = 15); and headache, nausea, and vomiting (50.0% each [7 of 14 subjects]), leukocytosis (42.9% [6 of 14 subjects]), pyrexia and cough (35.7% each [5 of 14 subjects]) in the antibody-positive subgroup (n = 14). Adverse events with a ≥20% higher incidence in the antibody-positive subjects than in the antibody-negative subgroup were nausea and vomiting (50.0% [7 of 14 subjects] in the antibody-positive subgroup vs. 20.0% [3 of 15 subjects] in the antibody-negative subgroup), and retinal tear (21.4% [3 of 14 subjects] vs. 0% [0 of 15 subjects]). Adverse events with a ≥20% higher incidence in the antibody-negative subgroup than in the antibody-positive subgroup were oropharyngeal pain (7.1% [1 of 14 subjects] vs. 40.0% [6 of 15 subjects]), and nasopharyngitis (14.3% [2 of 14 subjects] vs. 40.0% [6 of 15 subjects]). The incidence of retinal tear, an ocular adverse event, was ≥20% higher in the antibody-positive subgroup than in the antibody-negative subgroup, and all of them were non-serious and mild or moderate in severity. All of the events were assessed as unrelated to Luxturna but related to the injection procedure. The presence or absence of baseline anti-AAV2 antibodies did not show any tendency toward clear difference in the incidence of adverse events, although the small number of subjects studied poses limitations in the interpretation of the results.

(c) Luxturna is a gene therapy product administered to the eye topically. Since the eye is thought to be an immune-privileged site (*Nat Rev Immunol.* 2003;3:879-89), systemic immune reactions are unlikely to affect the efficacy or safety of Luxturna which acts in the eye. No adverse events related to host immune responses were observed in clinical studies.

(d) Luxturna is approved in ≥40 countries or regions as of the end of August 2022, and all of the regulatory agencies have concluded that it is unnecessary to check for anti-AAV2 antibody titer before Luxturna administration.

PMDA accepted the above explanation of the applicant.

7.R.6 Dosage and administration or method of use

The proposed “Dosage and Administration or Method of Use” and “Precautions Concerning Dosage and Administration or Method of Use” were as follows:

Dosage and Administration or Method of Use

The usual dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered as a single subretinal injection in a total volume of 0.3 mL. Subretinal administration of Luxturna to each eye should be performed on separate days within a close interval, with no fewer than 6 days apart.

Precautions Concerning Dosage and Administration or Method of Use

Regimen for pre- and post-operative administration of prednisolone (or equivalent dose of corticosteroids)

(1) The patient must be checked for symptoms of infectious disease before the initiation of administration of prednisolone (or equivalent dose of corticosteroids) and before the administration of Luxturna. If infection is detected, do not initiate the administration of prednisolone until the patient has recovered.

(2) Starting 3 days before the administration of Luxturna to the first eye, it is recommended that the administration of prednisolone is initiated according to the table below. Initiation of prednisolone to the second eye should follow the same schedule as the prednisolone dosing regimen for the first eye. If the administration of prednisolone to the first eye has not been completed, the schedule for administration of prednisolone to the second eye precedes completion of prednisolone regimen for the first eye.

Table Regimen for prednisolone administration

Pre-operative	3 days before Luxturna administration	Prednisolone 1 mg/kg/day (maximum of 40 mg/day)
Post-operative	4 days (including the day of Luxturna administration)	Prednisolone 1 mg/kg/day (maximum of 40 mg/day)
	Followed by 5 days	Prednisolone 0.5 mg/kg/day (maximum of 20 mg/day)
	Followed by 5 days of one dose every other day (Days 1, 3, and 5)	Prednisolone 0.5 mg/kg/every other day (maximum of 20 mg/day)

Procedures for preparation and subretinal administration of Luxturna

(3) Before administration, dilute Luxturna 10-fold with the dedicated diluent. Pay attention to the following points in the preparation and subretinal administration of Luxturna. For the details of the series of steps from preparation to administration, refer to the pharmacy and surgical manuals provided by the marketing authorization holder (see the “Storage method, shelf life, etc.” section).

1) Prepare Luxturna under aseptic conditions in a Class II biological safety cabinet (“safety cabinet”).
2) Thaw the frozen drug product and the dedicated diluent at room temperature to prepare the solution within 4 hours before the administration of Luxturna. Do not re-freeze the thawed drug product and the dedicated diluent.
3) Prepare Luxturna according to the prescribed procedure, using the specified syringe and needle.
4) Before surgery, dilate the pupil of the patient, give adequate anesthesia to the patient, and administer a wide-spectrum antibiotic to the conjunctiva, cornea, and palpebra of the patient.
5) Inspect Luxturna for its appearance before administration. If particulate matters, cloudiness, or discoloration are visible, do not use the syringe of Luxturna.
6) After completing a vitrectomy, inject Luxturna, preferably at the site ≥2 mm distal to the center of the fovea (see “2. Important Precautions” section).
7) Administer Luxturna under aseptic conditions.
8) Use the specified subretinal injection cannula and extension tube to administer Luxturna according to the prescribed procedure.
9) Inject Luxturna slowly until a subretinal bleb is observed. Then, inject the total 0.3 mL of Luxturna in the same manner.

10) Initiate supine head positioning immediately after the surgery.

11) Advise the patient to rest in the supine position as much as possible for 24 hours.

(4) Seal and discard unused Luxturna solution, vials, injection syringe, etc., as infectious wastes according to the procedures specified at each medical institution.

On the basis of reviews in Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4 Clinical positioning of Luxturna" and the review presented below, PMDA concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections of Luxturna should be modified as follows:

Dosage and Administration or Method of Use (Underline denotes additions or changes. Strikethrough denotes deletions.)

The usual dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered by a single subretinal injection in a total volume of 0.3 mL. Subretinal administration of Luxturna is to each eye should be performed on separate days within a close interval, ~~with~~ but no fewer than 6 days apart. No repeated administration of Luxturna to the same eye is allowed.

Precautions Concerning Dosage and Administration or Method of Use (Underline denotes additions or changes. Strikethrough denotes deletions.)

Regimen for pre- and post-operative administration of prednisolone (or equivalent dose of corticosteroids) to reduce the risk of immune responses to the capsid protein of Luxturna and RPE65 protein

(1) The patient must be checked for symptoms of infectious disease before the initiation of administration of prednisolone (or equivalent dose of corticosteroids) and before the administration of Luxturna. If infection is detected, ~~do not initiate~~ discontinue the administration of prednisolone. Administer prednisolone and Luxturna after ~~until~~ the patient has recovered.

(2) Starting 3 days before the administration of Luxturna to the first eye, ~~it is recommended that~~ the administration of prednisolone should be initiated according to the table below. Initiation of administration of prednisolone to the second eye should follow the same schedule as the prednisolone dosing regimen for the first eye. If the administration of prednisolone to the first eye has not been completed, the schedule for administration of prednisolone to the second eye precedes completion of prednisolone dosing for the first eye.

Table Regimen for prednisolone administration

Pre-operative	3 days starting at 3 days before Luxturna administration	Prednisolone 1 mg/kg/day (maximum of 40 mg/day)
Post-operative	4 days (including the day of Luxturna administration)	Prednisolone 1 mg/kg/day (maximum of 40 mg/day)
	Followed by 5 days	Prednisolone 0.5 mg/kg/day (maximum of 20 mg/day)
	Followed by 5 days of one dose every other day (Days 1, 3, and 5)	Prednisolone 0.5 mg/kg/every other day (maximum of 20 mg/day)

Procedures for preparation and subretinal administration of Luxturna

(3) Before administration, dilute Luxturna 10-fold with the dedicated diluent. Use proper aseptic techniques for the preparation and subretinal administration of Luxturna. In addition, pay attention

to the following points ~~in the preparation and subretinal administration of Luxturna~~. For the details of the series of steps from preparation to administration and the details of the instruments used, refer to the ~~pharmacy and surgical~~ manuals etc. ~~for preparation and surgery~~ provided by the marketing authorization holder (see the "Storage method, shelf life, etc." section)

~~1) Prepare Luxturna under aseptic conditions in a Class II biological safety cabinet ("safety cabinet").~~

2) Thaw the frozen drug product and the dedicated diluent at room temperature to prepare the solution. Complete the administration of Luxturna within 4 hours ~~before the administration of Luxturna administration~~ after thawing. Do not re-freeze the thawed drug product and the dedicated diluent.

~~3) Prepare Luxturna according to the prescribed procedure, using the specified syringe and needle.~~

4) Before surgery, dilate the pupil of the patient, give adequate anesthesia to the patient, and administer a wide-spectrum antibiotic to the conjunctiva, cornea, and palpebra of the patient.

5) Inspect Luxturna for its appearance before administration. If particulate matters, cloudiness, or discoloration are visible, do not use the syringe of Luxturna.

6) After completing a vitrectomy, inject Luxturna in the area located along the superior vascular arcade, preferably at the site ≥2 mm distal to the center of the fovea ~~(see "2. Important Precautions" section)~~.

~~7) Administer Luxturna under aseptic conditions.~~

~~8) Use the specified subretinal injection cannula and extension tube to administer Luxturna according to the prescribed procedure.~~

9) Inject a small volume of Luxturna slowly until a subretinal bleb is observed. Then, continue injecting the total 0.3 mL of Luxturna in the same manner.

10) Initiate supine head positioning immediately after the surgery.

11) Advise the patient to rest in the supine position as much as possible for 24 hours.

(4) Seal and discard unused Luxturna solution, vials, injection syringe, etc., as infectious wastes according to the procedures specified at each medical institution.

7.R.6.1 Dosage and administration or method of use of Luxturna

The applicant's explanation about the rationale for the "Dosage and Administration or Method of Use" for Luxturna:

The dosage and administration or method of use for Luxturna was determined based on the results of the phase I studies (Studies 101 and 102) and the phase III studies (Studies 301 and A11301).

The results of non-clinical studies suggested that doses exceeding 1.5×10^{11} vg/150 µL potentially lead to the increased risk of dose-limiting toxicity at high vector concentrations, while failing to show the clear evidence of increased efficacy. Thus, in Study 101, Luxturna was administered as a single subretinal injection to one eye at a dose of 1.5×10^{10} vg/150 µL, 4.8×10^{10} vg/150 µL, or 1.5×10^{11} vg/300 µL. No adverse events were assessed as related to Luxturna at any of the doses, showing no significant difference in the safety profile among the doses. Efficacy data showed improvement in visual function in all dose cohorts, but no clear dose response among the dose cohorts. Compared to the volume of 150 µL used in the low- and medium-dose cohorts, the volume of 300 µL used in the high-dose cohort was more likely to provide the direct benefit to subjects by allowing Luxturna to

spread to a wider extent of the retina. Accordingly, the dose of 1.5×10^{11} vg/300 μL was used in Study 102 (the extension study of Study 101) and Study 301.

In light of the safety and efficacy results of Studies 101 and 102 and the results of the non-clinical studies, subretinal injection into both eyes was considered to be an appropriate method for administration. The interval of 6 to 18 days between the first-eye and the second-eye injections was selected, by taking into account the following matters: (1) Time to identify surgical complications that may occur early after subretinal injection, specifically, between injections of Luxturna into one eye and the other eye; and (2) time to minimize the risk of adverse immune responses associated with enhancement of immune reactions to AAV that may result from a wider interval between injections.

In Study A11301 involving Japanese patients with biallelic *RPE65* mutation-associated IRD, Luxturna was administered as a single subretinal injection at a dose of 1.5×10^{11} vg/300 μL according to the dosage regimen used in Study 301, with the injection interval of 6 to 18 days between the first-treated eye and the second-treated eye. The applicant considered that the dosage regimen was applicable to Japanese patients and the use of the same dosage regimen as that in Study 301 was appropriate for the following reasons: (1) There is no anatomical-physiological difference in the size of eyeballs or the structure of the posterior eye segment between Japanese and non-Japanese; and (2) Luxturna is a gene therapy product for topical application and its efficacy is less susceptible to ethnic influence.

The efficacy results of Study A11301 were generally similar to those of Study 301, despite the limitation in the interpretation of efficacy and safety results because of the extremely small number of Japanese patients enrolled in Study A11301. The safety results were similar to those obtained so far on Luxturna, with no safety concerns specific to Japanese patients.

Thus, based on the results of the clinical studies, the applicant determined that the recommended dosage regimen for Luxturna is “The usual dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered as a single subretinal injection in a total volume of 0.3 mL. Subretinal administration of Luxturna to each eye should be performed on separate days within a close interval, with no fewer than 6 days apart.”

The interval between injections into the first eye and the second eye was defined as ≥6 days, for the following rationale: (1) the injection interval ranged from 6 to 18 days in Studies 301 and A11301; (2) the interval of corticosteroid administration should be reduced; and (3) it is necessary to shorten the duration of period when the visual function differs between the first-eye and second-eye injections. The upper limit of the injection interval was not specified, with consideration given to issues in clinical practice, such as the availability of the operating room in medical institutions, convenience of healthcare professionals, and conditions of patients.

PMDA’s view:
The applicant’s explanation is generally acceptable. Regarding the dosage regimen, the phrase “on separate days within a close interval” and the phrase “no fewer than 6 days apart” appear contradictory to each other. The description should be modified in an appropriate manner. In addition, the injection

interval employed in the clinical studies should be addressed in the “Clinical Studies” section of the package insert to provide information.

7.R.6.2 Use of corticosteroid

The applicant’s explanation about oral corticosteroid use before and after Luxturna administration:
In the clinical studies of Luxturna, oral corticosteroid was used before and after the subretinal injection of Luxturna into each eye to reduce the risk of immune responses to the capsid protein of Luxturna and RPE65 protein. There were no serious safety concerns such as immunogenicity and endophthalmitis. The “Precautions Concerning Dosage and Administration or Method of Use” section will include a statement to the effect that oral corticosteroid is used before and after the subretinal injection of Luxturna into each eye according to the dosage regimen used in the clinical studies.

PMDA accepted the above explanation of the applicant.

7.R.6.3 Re-administration in the same eye

PMDA asked the applicant to explain whether it is appropriate to re-administer Luxturna to the same eye.

The applicant’s response:
Re-administration of Luxturna to the same eye is not recommended because there have been no such cases either in the clinical studies or in foreign post-marketing experience. However, it is considered unnecessary to include in the package insert a statement to the effect that re-administration of Luxturna is not recommended, for the following reasons: (1) The “Dosage and Administration or Method of Use” section clearly states that Luxturna is for single-dose administration; and (2) the use of Luxturna is limited to physicians and surgeons with sufficient knowledge and experience in the diagnosis and treatment of retinal diseases including IRD, and they will be well informed of the proper use of Luxturna.

PMDA’s view:
Re-administration to the same eye is not recommended, because (1) Luxturna has never been re-administered to the same eye either in clinical studies or in foreign post-marketing experience; (2) the efficacy and safety of Luxturna re-administered are unknown; and (3) there are risks associated with Luxturna administration. In order to advise appropriate caution, the “Dosage and Administration or Method of Use” section should clearly state that Luxturna should not be re-administered to the same eye.

8. Risk Analysis and Outline of the Review Conducted by PMDA

The applicant’s explanation about the plan for the post-marketing surveillance on Luxturna:
After the launch of Luxturna on the market, the applicant plans to conduct, in addition to the extended Japanese Study A11301, a post-marketing surveillance involving all patients treated with Luxturna in order to investigate the safety and efficacy of Luxturna in clinical settings. This surveillance will be conducted as part of the long-term observational surveillance common to Japan, Europe, and elsewhere (survey code, Study A12401).

Safety specifications will include the following, based on the incidences of adverse events reported in the clinical studies and the foreign post-marketing data, as risks expected to occur in the post-marketing setting: “Intraocular pressure increased,” “retinal tear,” “retinal detachment,” “macular disease,” “cataract,” “injection procedure-related endophthalmitis or eye infection intraocular,” “tumorigenicity,” “host immune response,” “transmission to the third party,” and “vision loss caused by progressive chorioretinal atrophy.” In addition, the following will be included as missing information on Luxturna: “Use in pregnant and breast-feeding women,” “Use in children aged <3 years,” and “long-term safety.”

The planned sample size is 15, with consideration given to the expected number of patients who use Luxturna in the post-marketing setting.

The observation period will be 5 years after Luxturna administration for evaluation of specifications of the surveillance.

PMDA’s view:
Because of the extremely limited experience with the use of Luxturna in Japanese patients, a post-marketing surveillance should be conducted covering all patients treated with Luxturna in order to collect information on the safety and efficacy of Luxturna in a prompt and unbiased manner. The safety information thus obtained should be promptly provided to healthcare professionals.

The safety specifications and the observation period are acceptable as proposed by the applicant. Enrollment of new patients should be continued even after the target sample size of 15 has been reached, in order to collect as much safety information as possible. Details of the surveillance will be finalized, taking account of comments from the Expert Discussion.

9. Regulations on Type-1 Use of Living Modified Organisms under Article 4 of the Act on Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (“the Cartagena Act”)

The use of Luxturna is classified as Type-1 Use of Living Organisms under Article 4 of the Cartagena Act, and the Regulations on Type-1 Use of Living Organisms has been approved under the same article of the Act (Approval No. 22-36V-0013).

10. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

10.1 PMDA’s conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. Its results and the conclusion of PMDA will be reported in the Review Report (2).

10.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. Its results and the conclusion of PMDA will be reported in the Review Report (2).

11. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Luxturna has efficacy in the treatment of biallelic *RPE65* mutation-associated inherited retinal dystrophy, and that Luxturna has acceptable safety in view of its benefits. PMDA considers it meaningful to provide patient access to Luxturna as an option for the treatment of biallelic *RPE65* mutation-associated IRD.

PMDA has concluded that Luxturna may be approved if Luxturna is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 9, 2023

Product Submitted for Approval

Brand Name	Luxturna Injection
Non-proprietary Name	Voretigene neparvovec
Applicant	Novartis Pharma K.K.
Date of Application	September 30, 2022

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of the review in Section "7.R.2 Efficacy" of the Review Report (1), the following findings were obtained: (1) A statistically significant difference was observed in the MLMT score using both eyes, the primary endpoint, between treatment groups in Study 301 involving non-Japanese patients with biallelic *RPE65* mutation-associated IRD; (2) FST, the secondary endpoint, showed a tendency toward a greater improvement in the Luxturna group than in the control group in the above study; and (3) in Study A11301 involving Japanese patients with biallelic *RPE65* mutation-associated IRD, the primary endpoint FST showed a result suggestive of the efficacy of Luxturna. PMDA, therefore, concluded that the efficacy of Luxturna has been demonstrated to a certain extent in patients with biallelic *RPE65* mutation-associated IRD.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the review in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring special attention in treatment with Luxturna are ocular adverse events related to the injection procedure (cataract, intraocular pressure increased, macular disease, retinal tear and retinal detachment, injection procedure-related endophthalmitis or eye infection intraocular, vision loss caused by progressive chorioretinal atrophy), and that close attention should be paid to the risk of these adverse events in patients treated with Luxturna. On the other hand, there have been no serious

safety concerns considered to be related to Luxturna. Given this, Luxturna is tolerable, provided that appropriate measures, such as monitoring and management of adverse events, are taken by a physician with sufficient knowledge and experience in subretinal surgery at a medical institution well-equipped for responding to these adverse events.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Indication or performance

As a result of the review in Section "7.R.5 Indication or performance" of the Review Report (1), PMDA has concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections should be described as per the relevant sections of the Review Report (1). The criteria for the sufficient viable retinal cells specified in Studies 301 and A11301 should be addressed in the "Clinical Studies" section of the package insert to provide information.

The following comments were raised from the expert advisors at the Expert Discussion:

- PMDA's conclusion is generally supportable. The criteria for the sufficient viable retinal cells employed in Studies 301 and A11301 were intended for use in patients aged ≥3 years, and may not be uniformly applicable to all patients because children aged <3 years are also included in those eligible for treatment with Luxturna. The criteria employed in the clinical studies should be addressed in the package insert and materials just as information so that the attending physician can identify the eligibility of patients properly.

Following the above comments from the expert advisors, PMDA instructed the applicant to address the above criteria employed in the clinical studies in the package insert and materials just as information so that the attending physician can identify the eligibility of patients properly, and to modify the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections as shown below. The applicant responded to the instruction appropriately, and PMDA accepted the applicant's response.

Indication or Performance

Biallelic *RPE65* mutation-associated inherited retinal dystrophy

Precautions Concerning Indication or Performance

(1) Luxturna should be administered to patients with biallelic *RPE65* mutation confirmed by genetic testing.
(2) Luxturna should be administered to patients who are confirmed to have sufficient viable retinal cells by an appropriate test.

1.4 Dosage and administration or method of use

As a result of the review in Section "7.R.6 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections should be modified

as described in the relevant section of the Review Report (1), and the modified statements are as follows.

Dosage and Administration or Method of Use

The usual dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered as a single subretinal injection in a total volume of 0.3 mL. Subretinal administration of Luxturna to each eye should be performed on separate days within a close interval, but no fewer than 6 days apart. No repeated administration of Luxturna to the same eye is allowed.

Precautions Concerning Dosage and Administration or Method of Use

Regimen for pre- and post-operative administration of prednisolone (or equivalent dose of corticosteroids) to reduce the risk of immune responses to the capsid protein of Luxturna and RPE65 protein

(1) The patient must be checked for symptoms of infectious disease before the initiation of administration of prednisolone (or equivalent dose of corticosteroids) and before the administration of Luxturna. If infection is detected, discontinue the administration of prednisolone. Administer prednisolone and Luxturna after the patient has recovered.

(2) Starting 3 days before the administration of Luxturna to the first eye, the administration of prednisolone should be initiated according to the table below. Initiation of administration of prednisolone to the second eye should be follow the same schedule as the prednisolone dosing regimen for the first eye. If the administration of prednisolone to the first eye has not been completed, the schedule for administration of prednisolone to the second eye precedes completion of prednisolone dosing for the first eye.

Table Regimen for prednisolone administration

Pre-operative	3 days starting at 3 days before Luxturna administration	Prednisolone 1 mg/kg/day (maximum of 40 mg/day)
Post-operative	4 days (including the day of Luxturna administration)	Prednisolone 1 mg/kg/day (maximum of 40 mg/day)
	Followed by 5 days	Prednisolone 0.5 mg/kg/day (maximum of 20 mg/day)
	Followed by 5 days of one dose every other day (Days 1, 3, and 5)	Prednisolone 0.5 mg/kg/every other day (maximum of 20 mg/day)

Procedures for preparation and subretinal administration of Luxturna

(3) Before administration, dilute Luxturna 10-fold with the dedicated diluent. Use proper aseptic techniques for the preparation and subretinal administration of Luxturna. In addition, pay attention to the following points. For the details of the series of steps from preparation to administration and the details of the instruments used, refer to the manuals etc. provided by the marketing authorization holder (see the “Storage method, shelf life, etc.” section).

1) Thaw the frozen drug product and the dedicated diluent at room temperature to prepare the solution. Complete the administration within 4 hours after thawing. Do not re-freeze the thawed drug product and the dedicated diluent.
2) Before surgery, dilate the pupil of the patient, give adequate anesthesia, and administer a wide-spectrum antibiotic to the conjunctiva, cornea, and palpebra of the patient.

3) Inspect Luxturna for its appearance before administration. If particulate matters, cloudiness, or discoloration are visible, do not use the syringe of Luxturna.
4) After completing a vitrectomy, inject Luxturna in the area located along the superior vascular arcade, preferably at the site ≥2 mm distal to the center of the fovea.
5) Inject a small volume of Luxturna slowly until a subretinal bleb is observed. Then, continue injecting the total 0.3 mL of Luxturna in the same manner.
6) Initiate supine head positioning immediately after the surgery.
7) Advise the patient to rest in the supine position as much as possible for 24 hours.

(4) Seal and discard unused Luxturna solution, vials, injection syringe, etc., as infectious wastes according to the procedures specified at each medical institution.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA requested the applicant to modify the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections as described above. As the applicant appropriately responded to the request, PMDA accepted the response.

1.5 Post-marketing surveillance plan (draft)

At the time of regulatory submission, the applicant proposed a plan for post-marketing surveillance covering all patients treated with Luxturna to evaluate the safety and other aspects of Luxturna used in clinical settings. The planned sample size was 15. The planned observation period was 5 years.

As a result of the review in Section "8. Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), PMDA has concluded that enrollment of new patients should be continued even after the target sample size of 15 has been reached, so that as much safety information as possible can be collected.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA requested the applicant to modify the post-marketing surveillance plan based on the results of the Expert Discussion. In response, the applicant submitted an outline of the post-marketing surveillance plan (draft) shown in Table 47, and PMDA accepted the draft plan.

Table 47. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate the safety of Luxturna in routine clinical practice
Survey method	All-case surveillance
Population	Japanese patients with biallelic *RPE65* mutation-associated IRD
Observation period	5 years
Planned sample size	15 patients (patient enrollment will be continued during the enrollment period up to December 2027 even after the enrollment of 15 patients)
Main survey items	Safety specifications: Intraocular pressure increased, retinal tear, retinal detachment, macular disease, cataract, endophthalmitis or infection intraocular related to the injection procedure, tumorigenicity, host immune response, transmission to the third party, vision loss caused by progressive chorioretinal atrophy, use in pregnant or breast-feeding women, use in children aged <3 years, long-term safety

1.6 Other

1.6.1 Designation of specified regenerative medical product

In accordance with the "Principles for designation of biological products, specified biological products, and designated regenerative medical products" (PFSB/ELD Notifications No. 1105-1 and 1105-2 dated November 5, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare), PMDA has concluded that there is no need to designate Luxturna as a designated regenerative medical product because: (1) the risk of infection by adventitious agents derived from biological components of human or animal origin used for the manufacture of Luxturna is negligible; and (2) the risk of infection propagation caused by the use of Luxturna in the open system is negligible.

2. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new regenerative medical product application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new regenerative medical product application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication or performance as well as dosage and administration or method of use as below, with the following approval conditions, on the premise that the provision of cautionary advice via the package insert and the dissemination of information on the proper use of the product are appropriately implemented in the post-marketing setting. Because the product has the orphan regenerative medical product designation, the re-examination period should be 10 years. The product need not be designated as a designated regenerative medical product.

Indication or Performance

Biallelic *RPE65* mutation-associated inherited retinal dystrophy

Dosage and Administration or Method of Use

The usual dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered as a single subretinal injection in a total volume of 0.3 mL. Subretinal administration of Luxturna to each eye

should be performed on separate days within a close interval, but no fewer than 6 days apart. No repeated administration of Luxturna to the same eye is allowed.

Approval Conditions

1. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product until data from a certain number of patients have been accrued in order to understand the characteristics of patients using the product and to promptly collect safety and efficacy data, thereby taking necessary measures to ensure the proper use of the product.
2. The applicant is required to take necessary measures, such as disseminating the proper use guidelines prepared in cooperation with relevant academic societies, to ensure that physicians with adequate knowledge and experience in the treatment of inherited retinal dystrophy and surgeons with adequate knowledge, experience, and technique in subretinal (submacular) surgery fully understand relevant information, including results from clinical studies of the product and adverse events reported, and that the physicians and surgeons use the product in accordance with the “Indication or Performance” and “Dosage and Administration or Method of Use” at medical institutions well equipped for providing medical care for inherited retinal dystrophy.
3. The applicant is required, in order to ensure that the product is used in compliance with the regulations on Type-1 Use approved under the “Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003),” to take necessary measures such as announcement of the regulations on Type 1 Use.

Appendix

List of Abbreviations

AAV	adeno-associated virus
BAV	bovine adenovirus
BGH	bovine growth hormone
BPV	bovine parvovirus
[redacted]	[redacted]
BSE	bovine spongiform encephalopathy
BT cells	bovine turbinate cells
BTV	bluetongue virus
BVDV	bovine viral diarrhea virus
CBA	chicken beta actin
cDNA	complementary DNA
[redacted]	[redacted]
CI	confidence interval
CLIA	clinical laboratory improvement amendments
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CQA	critical quality attribute
EBV	Epstein-Barr virus
ECLIA	electrochemiluminescence immunoassay
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunosorbent spot
EOP	end of production cell
ERG	electroretinography
ETDRS	early treatment diabetic retinopathy study
FAS	full analysis set
FBS	fetal bovine serum
FDA	US Food and Drug Administration
FST	full-field light sensitivity threshold
gDNA	genomic DNA
HAV	hepatitis A virus
HBV	hepatitis B virus
HCP	host cell protein
HCV	hepatitis C virus
HEK293 cells	human embryonic kidney 293
HeLa cells	human cervical cancer cells
HHV	human herpes virus
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HSV	herpes simplex virus
HTLV	human T-cell leukemia virus
IFN-γ	interferon-gamma
IRD	inherited retinal dystrophy
ITR	inverted terminal repeat
ITT	intention-to-treat
LCA	Leber Congenital Amaurosis
LOD	limit of detection
logMAR	logarithmic minimum angle of resolution (Logarithm of the minimal visual angle (in minute) formed by 2 lines from the eye to 2 barely discernible points)
LOQ	limit of quantification
Luxturna	Luxturna Injection

MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
MLMT	multi-luminance mobility test
MRC-5 cells	human fetal lung fibroblast cells
MTVS study	Mobility Test Validation Study
OCT	optical coherence tomography
PAV	porcine adenovirus
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PCV	porcine circovirus
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PNQ	positive non-quantitative
PPV	porcine parvovirus
PT	preferred term
PT-1	porcine testis cells
PVB19	parvovirus B19
qPCR	quantitative polymerase chain reaction
RABV	rabies virus
rcAAV	replication competent AAV
Regulatory submission	Submission of application for marketing approval
Reo	reo virus
RP	retinitis pigmentosa
RPE	retinal pigment epithelium
RSV	respiratory syncytial virus
[redacted]	[redacted]
SFV	simian foamy virus
SOC	system organ class
Spark	Spark Therapeutics, Inc.
SRV	simian retrovirus
STLV	simian T-lymphotropic virus
SV40	simian virus 40
[redacted]	[redacted]
TGEV	transmissible gastroenteritis virus
Vero cells	African green monkey kidney epithelial cells
vg	vector genome
WHO	World Health Organization