NOVARTIS

Patient Safety & Pharmacovigilance

Voretigene Neparvovec

LTW888A1

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	AAV2-hRPE65v2 voretigene neparvovec
Product(s) concerned (brand name(s)):	Luxturna
Document status:	Final
Version number:	3.2
Data lock point for this RMP	23-Jul-2023
Date of final sign off	11-June-2024

Template version 6.4, Effective from 12-Dec-2023

Rationale for submitting an updated RMP:

The RMP v3.2 is updated to address the list of questions received from EMA following the submission of the EU RMP v3.1.(Procedure Nr. EMEA/H/C/004451/IB/0047)

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v3.0
Part I	No change.
Part II	Module SV: No change Module SVII: Table 8.3.1.1 is updated with a minor editorial change.
Part III	No change.
Part IV	No change
Part V	No change
Part VI	Minor editorial changes.
Part VII	Annex 1: No change. Annex 2: No change. Annex 3: No change Annex 4: No change Annex 5: No change. Annex 6: No change. Annex 7: No change. Annex 8: Summary of changes are updated.

Other RMP versions under evaluation

No other RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 2.1

Approved with procedure: EMEA/H/C/004451/IB/0028

Date of approval (opinion date): 28-Feb-2022

QPPV name: Dr Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of abbreviations

AAV	Adeno-associated virus
AAV2	AAV vector serotype 2
ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CβA	Chicken β-actin
CMV	Cytomegalovirus
EEA	European Economic Area
EMA	European Medicines Agency
EORD	Early onset retinal dystrophy
EOSRD	Early onset severe retinal dystrophy
EPAR	European Public Assessment Report
ERG	Electroretinogram
EU	European Union
FDA	Food and Drug Administration
FST	Full-field light sensitivity threshold
HDE	Humanitarian Device Exemption
hRPE65	Human retinal pigment epithelium 65kDa protein
INN	International non-proprietary name
IOP	Intraocular pressure
ITR	Inverted terminal repeat
LCA	Leber congenital amaurosis
LTFU	Long-term follow-up
MA	Marketing Authorization
MAH	Marketing Authorization Holder
NHP	Non-human primate
OCT	Optical Coherence Tomography
PASS	Post-authorization safety study
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RP	Retinitis pigmentosa
SD	Standard deviation
SECORD	Severe early childhood onset retinal dystrophy
SmPC	Summary of Product Characteristics
US	United States
VA	Visual acuity
vg	Vector genomes

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	AAV2-hRPE65v2 voretigene neparvovec
Pharmacotherapeutic group(s) (ATC Code)	S01XA27
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Luxturna
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Recombinant adeno-associated viral (AAV) vector serotype 2 capsid used as a delivery vehicle for the human retinal pigment epithelium 65 kDa protein (hRPE65) cDNA.
	Summary of mode of action: Voretigene neparvovec employs AAV as a delivery vehicle for the normal human RPE65 cDNA; the recombinant vector is a non-enveloped icosahedral virion of approximately 26 nm in diameter. The parent virus AAV serotype 2, used as a template for the vector, is a non-pathogenic, single- stranded DNA genome-containing, helper virus-dependent member of the parvovirus family.
	Important information about its composition: The AAV vector sequence encoded by pAAV.CMV.CβA.hRPE65v2 contains the chicken β-actin (CβA) promoter driving expression of cDNA encoding retinal pigment epithelium 65kDa protein (RPE65). CCI There are no other structural components in voretigene neparvovec.
Hyperlink to the Product Information	[Current approved SmPC]
Indication(s) in the EEA	Current:

	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.
	Proposed: Not applicable
Dosage in the EEA	Current: Patients will receive a dose of 1.5 x 10^{11} vector genomes (vg) voretigene neparvovec in each eye. Each 1.5 x 10^{11} vg dose will be delivered to the subretinal space in a total volume of 0.3 mL. The individual administration procedures will be performed on separate days within a close interval, but no fewer than 6 days apart.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Concentrate for solution for subretinal injection. Each mL of concentrate contains 5 x 10^{12} vg. Each vial of voretigene neparvovec contains 0.5 extractable mL of concentrate for solution for subretinal injection. After dilution, each dose of voretigene neparvovec contains 1.5 x 10^{11} vg of voretigene neparvovec in a deliverable volume of 0.3 mL.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication

Voretigene neparvovec 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.

RPE65 mutation-associated retinal dystrophy

Biallelic mutations in the *RPE65* gene lead to inherited retinal degenerative disease. The spectrum of disease due to these autosomal recessive mutations in *RPE65* exhibits a number of common clinical findings; however, depending on time of onset, severity, rate of disease progression, and presenting phenotype, individuals may have been categorized with different clinical diagnoses resulting from a reduced or absent level of RPE65 isomerohydrolase. This reduced or absent level of retinoid isomerohydrolase activity, encoded by *RPE65*, eventually leads to the accumulation of toxic precursors, reduced viability of the RPE cells and finally, loss of photoreceptors. Individuals with biallelic mutations in the *RPE65* gene have commonly been diagnosed with Leber congenital amaurosis (LCA), and have also been characterized clinically with early onset retinal dystrophy (EORD), early-onset severe retinal dystrophy (EOSRD), early childhood-onset retinitis pigmentosa (ECRP), severe early childhood onset

retinal dystrophy (SECORD), early onset retinitis pigmentosa, retinitis pigmentosa (RP), and other similar clinical diagnoses (Redmond et al 1998; Lorenz et al 2004; Walia et al 2010; Weleber et al 2011). Various forms of EORD are conditions with a slightly later onset than LCA. Some individuals with biallelic mutations in the *RPE65* gene exhibit a phenotype that is milder than that of classic LCA, although night blindness is present from a very early age, if not congenitally.

Some patients with autosomal recessive *RPE65* gene mutations may have been diagnosed with retinitis pigmentosa, a broader clinical classification for inherited retinal disease (Morimura et al 1998). RP is a heterogeneous form of inherited retinal disease exhibiting clinical features similar to LCA, but with a later onset of symptoms. RP is generally characterized by a progressive degeneration of rod and cone photoreceptors, but the age of onset and extent of vision loss is more variable than LCA. However, deficits in dark adaptation and peripheral vision loss in RP are similar to LCA and are characteristics of most forms of RP, regardless of inheritance pattern and genetic cause. Both LCA and RP can be diagnosed in patients with photoreceptor degeneration who may retain good central vision within the first decade of life, but with subsequent progression of the disease resulting in profound vision loss (Thompson et al 2000). Associated with both clinical diagnoses, there is a reduced or non-detectable electroretinogram, particularly the scotopic responses, even at early ages, as well as attenuated retinal blood vessels and varying amounts of pigmentary deposits within the retina in later stages of the disease process (Morimura et al 1998).

The lack of discriminating clinical features between LCA and early onset severe RP, together with the apparent overlap in their severity, suggests that LCA and RP are different clinical descriptors for the same genetic disease that can present across a spectrum of onset and clinical manifestations. Indeed, Dr. Theodore Leber, who first described LCA in the late nineteenth century, subsequently suggested that RP (first defined by Dr. Franciscus Donders in 1857) may be a milder form of the same disease (Leber, n.d.). We now know that these diseases can have the same pathophysiology: in the case of LCA2 and RP20, biallelic mutations in the *RPE65* gene, leading to a reduced or absent level of the isomerohydrolase activity, encoded by *RPE65*, that leads eventually to accumulation of toxic precursors, reduced viability of the RPE cells, and finally, loss of photoreceptors.

As genes are identified for more forms of inherited retinal dystrophy, and genetic diagnosis becomes more routinely available, the classification of these diseases is likely to shift from a clinical diagnosis, based on phenotypic presentation, to a DNA-based genetic diagnosis. This trend is likely to be accelerated by the availability of gene-based therapeutics.

Incidence and prevalence

Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) are clinical descriptors for inherited disease that primarily affects the retina. First signs of the condition can appear as soon as 2-3 months of age (American Association for Pediatric Ophthalmology and Strabismus, 2014).

Leber congenital amaurosis is estimated to affect ~1/81,000 individuals (Stone 2007). Mutations in the *RPE65* gene are identified in 8 to 16% of those diagnosed with this condition (Morimura et al 1998; Stone 2007; Thompson et al 2000; Simovich et al 2001; Astuti et al 2016).

Retinitis pigmentosa (RP) is estimated to affect approximately 1/3,500 to 1/4,000 individuals (Haim 2002). It is estimated that a range of 1 to 3% of all patients with RP have underlying genetic mutations in the *RPE65* gene (Morimura et al 1998; Thompson et al 2000; Wang et al 2014).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Both children and adults, and both males and females are affected. There is no specific ethnicity profile.

Risk factors for the disease

Leber congenital amaurosis and retinitis pigmentosa due to *RPE65* mutations usually have an autosomal recessive pattern of inheritance. If both parents are carriers (i.e. have one defective copy) of the gene, each of their children has a 25 percent (1 in 4) chance of inheriting both defective copies of the gene which would cause the disorder (Foundation Fighting Blindness 2015). Carriers generally do not show any signs or symptoms of the condition (Genetic Home Reference 2010; Foundation Fighting Blindness 2015). Currently, the carrier status is not typically identified before an affected child is born (Foundation Fighting Blindness 2015). There are rare reports of an autosomal dominant *RPE65* mutation-associated IRD (Bowne et al 2011), described as RP with choroidal involvement, which is not addressed in this clinical development program.

Main existing treatment options

At present, there are no other pharmacological treatments approved for *RPE65* mutation associated inherited retinal disease in any market known to the marketing authorization holder (MAH). Luxturna has been approved in the US by FDA on 19-Dec-2017 for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. One treatment for the indication RP (which includes patients with a clinical diagnosis of LCA), is a device product that received Humanitarian Device Exemption (HDE) approval from FDA in Feb-2013, and is now available in the US and the EU. The Argus® II Retinal Prosthesis System is indicated for patients with end-stage disease, i.e. blind patients with severe to profound RP and bare or no light perception in both eyes, regardless of the underlying genetic mutation. At least one other device is also available in the EU for patients with RP who are “completely blind” (Alpha IMS, Retina Implant AG). Additionally, the BrainPort® V100 non-surgical device is cleared for use in the US in individuals with no usable vision, both congenitally blind and with acquired blindness.

Voretigene neparvovec is a recombinant adeno-associated viral (AAV) vector serotype 2 capsid used as a delivery vehicle for the human retinal pigment epithelium 65 kDa protein (hRPE65) cDNA to the retina that acts as a disease modifier by providing a normal copy of the gene (i.e. gene augmentation) that is a causal factor in biallelic *RPE65* mutation-associated retinal dystrophy.

Mortality and morbidity (natural history)

About 10-18% of all cases of congenital blindness or severely reduced vision in children are caused by LCA (American Association for Pediatric Ophthalmology and Strabismus 2014).

LCA is usually diagnosed within the first few months of life and presents with severely impaired visual behaviour, abnormal eye movements (nystagmus), diminished pupillary light reflexes and abnormal ERGs indicative of decreased retinal function. Due to the death of photoreceptor cells, these patients inevitably progress to total blindness (Redmond et al 1998). Various forms of EORD have a later onset than LCA with some individuals with biallelic mutations in the RPE65 gene exhibiting a phenotype that is milder than classic LCA, however night blindness is present from a very early age if not from birth.

The onset of symptoms in RP is variable but usually begins between the ages of 10-30 although some changes may become apparent earlier in childhood. There is generally a progressive degeneration of rod and cone photoreceptors. The extent of vision loss is more variable than LCA, but deficits in dark adaptation and peripheral vision are similar to LCA. RP may be diagnosed in patients with photoreceptor degeneration who may retain good central vision in the first decade of life but then progress to profound vision loss (Thompson et al 2000). As a child gets older and by early adolescence, changes in the retina become more apparent and include narrowing and constriction of blood vessels, and a variety of pigmentary changes in the retinal pigment epithelium (Foundation Fighting Blindness 2015).

Concomitant medication(s) in the target population

This target population, which consists of children and adults, is usually otherwise healthy aside from the retinal disease. Concomitant medications are typically for treatment of coincidental comorbid conditions. The most commonly used medications include minor pain relief treatments and antipyretics (paracetamol, ibuprofen and aspirin [over 16 years of age]) and occasional use of antibiotics.

Important co-morbidities in the target population

There are usually no significant co-morbidities associated with this patient population.

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Non-clinical studies consisted of dog and non-human primate (NHP) models. Non-human primates were used due to the susceptibility of dogs to showing higher amounts of inflammation after surgical procedures compared to other animal models. Additionally, NHPs are similar to humans in that they have a macula. There is only one amino acid difference between RPE65 protein of humans and NHP compared to the dog model where there are eight differences and therefore NHPs are less likely to view human RPE65 as foreign.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Simultaneous bilateral administration of voretigene neparvovec was well tolerated in both normal and *RPE65* mutant dogs at the therapeutic dose, and in (normal sighted) non-human primates (NHPs) at five-fold the therapeutic dose. In addition, bilateral sequential subretinal administrations were well tolerated in dogs, even when subsequent injections were carried out several months after the first injection. Although not anticipated to be performed in the clinical setting, re-administration of voretigene neparvovec to a previously injected eye was also well tolerated.	No significant toxicity identified as relevant to human use.
Histopathological findings in the eye were mostly attributable to surgical trauma, though some inflammatory toxicity was observed, particularly in the dog model at the highest doses tested (1.5×10^{12} vg per eye [10-fold higher than the highest dose used in the clinical studies]). Ocular histopathology revealed inflammatory lesions consistent with toxicity and cell death of RPE cells, followed by degenerative activity. The vector used in this study (AAV2-hRPE65v1) was similar to the final vector; however, had a low transgene expression, and therefore the observed toxicity was considered likely due to the dose of AAV2 capsid rather than expression of the RPE65 protein. Histopathological findings in NHPs were milder. There was no evidence of a pro-inflammatory T-cell response to the AAV2 capsid or RPE65 protein in the NHP model, and a limited T-cell response to RPE65 was observed in dogs (CCI). Antibodies to RPE65 were only detected in isolated cases, either transiently or where negative serum sample controls were also positive. Antibodies (including neutralizing antibodies) to AAV2 capsid proteins were variously detected in the anterior chamber fluid or serum of both normal and affected dogs and in NHPs previously exposed to AAV2. Antibody subclass analysis performed in one study showed a predominant Th2 (T helper cell) response. Biodistribution of the vector in tissues was analyzed by qPCR at Day 92 in NHPs and at Week 3 and Month 3 in normal dogs; vector DNA was mainly localized to the intraocular fluids, with weak signals in the optic nerves and optic chiasm. There was no evidence of vector spread to the gonads, brain, or other tissues with the exception of spleen, and, to a lesser extent, the liver, which were positive for the test article in a dose-dependent manner.	Surgical trauma related to the procedure may have some relevance to human use. However, this is related to the procedure which is not unique to this product. These findings were not considered a safety issue for humans as the dog is considered a provocative model and these findings were seen at a dose 10 times higher than the proposed therapeutic dose in humans. Additionally, this was not seen in NHPs at 7.5×10^{11} vg/eye.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Carcinogenicity studies have not been conducted. However, in toxicity studies, no increase in tumor was identified. Although there is no fully adequate animal model to address the tumorigenic potential, the available toxicological data do not suggest any concern for tumorigenicity.	No significant area identified relevant to use in humans.
Bilateral, simultaneous subretinal administration of voretigene neparvovec was well tolerated at doses up to 8.25 x 10^{11} vg per eye in dogs and 7.5 x 10^{11} vg (5 times the recommended dose) per eye in non-human primates. Bilateral, sequential subretinal administrations, where the contralateral eye was injected following the first eye, were well tolerated at the recommended per eye dose (1.5 x 10^{11} vg). Ocular histopathology of dog and NHP eyes exposed to voretigene neparvovec at these doses showed only mild changes, which were mostly related to healing from surgical injury.	Animal studies show that re-injection to the same eye is safe in dogs; however, this has not been tested in humans. Administration to the contralateral eye did not highlight any specific unexpected issues.

The significant safety concerns from non-clinical studies that are relevant for human use are noted below.

Table 3-2 Significant safety concerns from non-clinical studies that are relevant for human use

Safety concerns
Important identified risks (confirmed by clinical data) • Findings related to surgical procedure • Focal inflammatory changes related to the surgical procedure
Important potential risks • Inflammatory events - dose dependent

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Voretigene neparvovec was initially tested in a Phase 1, open-label dose escalation safety study in patients with inherited retinal disease due to autosomal recessive *RPE65* gene mutations. Enrolment for the study, entitled "A Phase 1 Safety Study in Subjects with LCA Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 into the Retinal Pigment Epithelium (RPE) [AAV2-hRPE65v2-101]," began in October 2007 and was completed in Jun-2009. The primary objective of the Phase 1, open-label, dose escalation study (#101) was to determine the safety and tolerability of gene transfer by subretinal administration of voretigene neparvovec; a secondary objective was to assess both the objective and subjective clinical measures of efficacy in patients with *RPE65* gene mutations.

In Nov-2010, enrolment for a follow-on study, entitled "A Follow-On Study to Evaluate the Safety of Re-Administration of Adeno-Associated Viral Vector Containing the Gene for Human RPE65 to the Contralateral Eye in Subjects with LCA Previously Enrolled in a Phase 1 Study [AAV2-hRPE65v2-102]," began. Eleven of 12 subjects from the initial Phase 1 study (#101) transferred to the follow-on study (#102); one subject who participated in the #101 study was not eligible for the #102 study due to glaucoma in the contralateral eye. Enrolment for the follow-on study was closed in 2013. The primary objective of the Phase 1 follow-on study (#102) was to assess the safety and tolerability of non-simultaneous, bilateral subretinal administration of voretigene neparvovec (administration to the contralateral eye). Vector was delivered to the contralateral eye of subjects that previously enrolled in the Phase 1 study evaluating the safety and tolerability of unilateral, subretinal administration. The secondary objective was to evaluate the efficacy of administration of voretigene neparvovec to the contralateral eye, using as a control the pre-injection measurements of the eye. At the time of initiation of the #102 study (Nov-2010), all subjects had completed at least their Year One #101 study visit.

In Nov-2012, enrolment began for a Phase 3, randomized controlled study, entitled "A Safety and Efficacy Study in Subjects with LCA Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE) [AAV2-hRPE65v2-301]." The study, conducted at Children's Hospital of Philadelphia and University of Iowa, followed 29 participants that received voretigene neparvovec, including the 9 control subjects that crossed over to receive the intervention after one year of observation; the last subject enrolled in Nov-2013 and enrolment was formally closed after all study group randomization assignments (intervention or control) had been provided and all subjects had received near-simultaneous, bilateral administration of voretigene neparvovec (Apr-2014). The objectives of the Phase 3 (#301) study were to assess the safety, tolerability, and efficacy of sequential, bilateral, subretinal administration of voretigene neparvovec to subjects with *RPE65* gene mutations. In addition to monitoring for safety and tolerability in the stated population, efficacy was evaluated using a number of retinal and visual function tests. Standardized mobility testing was the primary efficacy endpoint. The primary objective was to determine whether near-simultaneous, bilateral subretinal administration of voretigene neparvovec improves the ability to navigate (as measured by mobility testing under a range of lighting conditions) in adults and children with *RPE65* gene mutations, 3 years of age or older. Mobility test performance one year following vector administration was compared to the subject's

pre-administration, baseline mobility test performance; independent, masked reviewers were trained to assess the ability to navigate.

The 41 subjects that have received voretigene neparvovec in the clinical program (Phase 1 and Phase 3) have transferred from the gene therapy protocols to a separate long-term follow-up (LTFU) protocol, AAV2-hRPE65v2-LTFU-01 in which they will be followed for 15 years post vector administration.

The tables presented in this section include the level of exposure and demographic data deriving from the 3 clinical trials sponsored by Spark Therapeutics, Inc.:

AAV2-hRPE65v2-101

In this Phase 1 dose-escalation trial, voretigene neparvovec was administered to a total of 12 subjects with *RPE65* gene mutations; subjects received a single, unilateral (one eye) dose of voretigene neparvovec by subretinal administration. Three subjects received a low dose (1.5×10^{10} vg in a volume of 0.15 mL), 6 subjects received a middle dose (4.8×10^{10} vg in a volume of 0.15 mL), and 3 subjects received a high dose (1.5×10^{11} vg in a volume of 0.3 mL).

AAV2-hRPE65v2-102

The study was a Phase 1 follow-on study of gene transfer by subretinal administration of voretigene neparvovec to the contralateral eye; eligible subjects received an injection of 1.5×10^{11} vg voretigene neparvovec in a total subretinal volume of 0.3 mL to the previously uninjected, contralateral eye. Out of 12 subjects with *RPE65* gene mutations who participated in Study #101, 11 eligible subjects had the second eye administration procedure.

AAV2-hRPE65v2-301

The study was a Phase 3, open-label, randomized controlled trial of gene therapy intervention by subretinal administration of voretigene neparvovec. Of the 36 enrolled subjects, 31 were determined to be eligible for randomization. Of the 31 eligible subjects, 10 were randomized to the control group and 21 were randomized to the intervention group. Of the 21 subjects in the intervention group, 20 (95%) received near-simultaneous injection of voretigene neparvovec and one subject discontinued the study early (prior to injection) due to physician decision. In the control group, one subject discontinued the study early due to withdrawn consent. One subject randomized to the intervention group was determined to be an eligibility violation 4 months following bilateral administration of voretigene neparvovec, based on screening visit mobility test performance. All control subjects completed one year of observation and subsequently crossed over to the intervention group and had bilateral administration of voretigene neparvovec. In Phase 3, 29 subjects (58 eyes) received 1.5×10^{11} vg of the vector in each eye, with a mean (SD) interval between the first and second injections of 8.4 (2.3) days (range 7 to 14 days).

Table 4-1 Exposure by dose (level of exposure)

Level of exposure	Number of administrations			
	#101	#102	#301[a]	Total
Low 1.5×10^{10} vg	3	0	0	3
Middle 4.8×10^{11} vg	6	0	0	6

Level of exposure	Number of administrations			
	#101	#102	#301[a]	Total
High 1.5×10^{10} vg	3	11	58	72
Number of administrations in each trial	**12**	**11**	**58**	**81**

[a] Includes 20 intervention subjects who received bilateral voretigene neparvovec injections in Study 301 and also 9 control subjects who subsequently crossed over after a year of observation and received bilateral voretigene neparvovec injections.

Table 4-2 Exposure by age group and gender

Age group (years)	Number of subjects			
	Male		Female	
	at first administration #101 and #102	at randomization #301	at first administration #101 and #102	at randomization #301
≤ 8	1	6	0	5
> 8 and ≤ 16	3	3	0	6
> 16 and ≤ 24	1	1	3	3
> 24 and ≤ 32	1	0	1	1
> 32	1	1	1	3
Total	**7**	**11**	**5**	**18**

Table 4-3 Exposure by racial origin and gender

Race	Number of subjects		
	Male	Female	Total
Caucasian	16	15 (including 3 Hispanic or Latino)	31
Asian	2	3	5
Black or Afro-American	0	2	2
American Indian or Alaskan native	0	3 (Including 3 Hispanic or Latino)	3

In addition, Study CLTW888A11301 is a local, Novartis-sponsored Phase 3 study being conducted in Japan to demonstrate safety and efficacy of voretigene neparvovec in the treatment of biallelic *RPE65* mutation-associated retinal dystrophy in Japanese patients. The study is designed as an open-label, single-arm study, enrolling up to four subjects in Japan aged four years or older. As of the data lock point (23-Jul-2023), 4 patients had been treated with voretigene neparvovec.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

The youngest subjects participating in the clinical study program were 4 years old and no younger children were recruited. Age less than 3 years old was an exclusion criterion due to difficulties associated with patient understanding and/or performance of efficacy measurements in this age group. Based on the natural course of development of the eye and extrapolation from clinical data, children as young as 12 months old may receive treatment.

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Children < 3 years old	Issues associated with ability of this age group to understand how to perform subjective clinical trial endpoint assessments. Additionally, there was concern about the surgical procedure in children < 3 years old.	Yes	NA
Individuals of childbearing potential who are pregnant or unwilling to use effective contraception for four months following vector administration.	This is a standard exclusion criterion for a clinical study and related to unknown risk of exposure in this patient population.	Yes	NA
Unable or unwilling to meet requirements of the study, including receiving bilateral subretinal vector administrations.	Only individuals willing to adhere to protocol and long-term follow-up as evidenced by written informed consent or parental permission and subject assent (where applicable) met the study eligibility criteria.	No	This exclusion criterion was to ensure validity of the study and is not missing information, as per RMP.
Any prior participation in a study in which a gene therapy vector was administered.	Due to potential confounding of the interpretation of the efficacy and safety results as well as a potential safety risk.	No	This exclusion criterion was to ensure validity of the study and is not missing information, as per RMP.
Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the RPE65 enzyme; individuals who	Due to potential confounding of the interpretation of the efficacy and safety results	No	This exclusion criterion was to ensure validity of the study and is not missing information, as per RMP.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
discontinue use of these compounds for 18 months may become eligible.			
Pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study. Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can alter ocular function. E.g. malignancies whose treatment could affect central nervous system function (for example: radiation treatment of the orbit; leukaemia with CNS/optic nerve involvement). Subjects with diabetes or sickle cell disease would be excluded if they had any manifestation of advanced retinopathy (e.g., macular oedema or proliferative changes).	Due to potential added safety risks with the planned surgery or the interpretation of study results. Ocular or periocular infection, and active intraocular inflammation will be contraindications as they would preclude the planned surgery. The surgery is non-urgent and can be performed when the patient does not have concurrent ocular or periocular infection and/or active intraocular inflammation.	No	Ocular or periocular infection, and active intraocular inflammation will be considered an important potential risk. The remainder were exclusion criteria to ensure validity of the study and would not be considered as missing information.
Subjects with immunodeficiency (acquired or congenital) as there could be susceptibility to opportunistic infection (such as CMV retinitis)	This was related to the use of prednisone / prednisolone in the study and the potential for immunosuppression.	No	This exclusion criterion relates to use of immunosuppressives in patients with immunodeficiency. Eye surgeries including vitrectomy and retinal repairs are performed on patients with immunodeficiencies. If infection or inflammation arises post-voretigene administration, it should be treated according to current standard-of-care for treatment for immunodeficient patients undergoing eye surgery. This is not missing information, as per RMP.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Individuals incapable of performing mobility testing (the primary efficacy endpoint) for reason other than poor vision, including physical or attentional limitations.	Eligibility criteria stated that eligible study subjects must be evaluable on mobility testing (the primary efficacy endpoint).	No	This exclusion criterion was related to evaluating efficacy within the study and is not missing information.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Table 5-2 Limitations to detect adverse reactions in clinical trial development programs

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	There were 41 subjects exposed across the whole clinical trial program.	The limited number of clinical trial participants does not allow the detection of rare ADRs.
Due to prolonged exposure	N/A this is a single administration per eye	N/A
Due to cumulative effects	This is a single administration per eye, however injections are given to both eyes in a near-simultaneous manner i.e. performed on separate days within a close interval, but no fewer than 6 days apart.	Non-clinical studies have shown no local or systemic toxicity with a repeat administration of product to the same eye. No clinically significant cytotoxic responses were seen.
Which have a long latency	A potential risk of insertional mutagenesis leading to tumorigenicity may not be detectable in the limited number of subjects and the current follow-up period of up to 7 to 9 years.	Although there have been reports of both ocular and non-ocular malignancies following the use of voretigene neparvovec in the clinical program, including the LTFU study, none of these events were assessed by the investigator as related to treatment with the study medication. Of note, one of the subjects treated with voretigene neparvovec died due to acute myeloid leukemia (AML) despite treatment.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

As reflected by this product having orphan drug status, there is a small population of affected individuals, making subject accrual challenging, particularly for a controlled study in this serious and progressive condition. As such, the overall number of patients receiving product in the clinical trial setting is low.

Table 5-3 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	No clinical studies were conducted in pregnant or lactating women. One pregnancy occurred in study 301. The subject was PPD years old at entry into the study and at the year 1 visit was noted to be 23 weeks pregnant without any known complications. The study participant gave birth to a full-term live infant with no congenital abnormalities approximately 1.5 years after vector administration. One male subject in the 101 study has fathered 4 children after receiving voretigene neparvovec. One child was born 2 years after, one 5 years after and twins 8 years after treatment, all of whom were healthy. Biodistribution outside of the eye is limited and was detectable in serum only up to three days post administration. With this limited systemic exposure, AAV infection of the fetus is highly unlikely.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Not applicable.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other Children	The product has been used in children ≥ 4 years old. Patients < 4 years old have not yet been exposed to product. Children < 3 years old were not able to perform the efficacy measures and therefore could not be included in the trials. Additionally, there was concern that the surgical procedure posed an increased risk in children < 3 years old. Since then, however surgical instruments and technique in pediatric retinal surgery have evolved and the surgical procedure is no longer considered to pose an increased risk in this age group.

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

The post-authorization exposure to voretigene neparvovec is based on the following methodology:

- Post-authorization data in the USA are based on the actual patient exposure, including specific details of unilateral and bilateral administration for the treated patients.
- Post-authorization data in the ex-USA territory under Novartis MA has been calculated based on the post-marketing sales data. The estimated exposure was calculated by dividing the overall number of vials sold by a factor of two based on the assumption that a majority of patients would receive bilateral treatment with voretigene neparvovec, unless contraindicated in one eye, to gain maximum clinical benefit.

6.1.2 Part II Module SV.1.2. Exposure

The post-authorization exposure data by region are shown in Table 6-1. Cumulatively, 15 patients received voretigene neparvovec treatment under MAH-sponsored managed access programs and have also been included in the post-authorization exposure.

Table 6-1 Cumulative exposure (number of patients [number of patient eyes]) from marketing experience by region

	EU/EEA**	ROW*	USA+
Voretigene neparvovec 1.5E11 vg/eye	256 [506]	121 [239]	223 [426]

EEA: European Economic Area; EU: European Union; ROW: Rest of the World; USA: United States of America; vg: vector genomes.

Cumulative exposure includes data obtained from 19-Dec-2017 through Jul-2023 for EU/EEA and ROW region while for USA data from Spark Therapeutics were obtained from 19 Dec 2017 through 23 Jul 2023.

+Cumulatively, 223 patient(s) in the USA received at least one voretigene neparvovec administration, including 203 patient(s) treated bilaterally and 20 patient(s) treated unilaterally.*Exposure data from United Kingdom and Canada has been included in ROW region

**The number of patients is calculated at country level by dividing number of vials by two (vials per patient). In case of an odd number of vials sold, data is rounded off to next digit considering the additional vial may correspond to a patient treated in one eye. Therefore, the total number of patients for the EU/EEA corresponds to 256

The post-authorization exposure data by age and gender for the patients treated in the USA is shown in Table 6-2. The ex-USA exposure data are estimated based on sales volume of commercial product and stratification by age and gender is not available for these data.

Table 6-2 Cumulative exposure from marketing experience in the USA by age and gender

		Cumulative exposure (number of patients)
Gender	Male	102
	Female	109
	Unknown	12
	Total	**223**
Age (years)	0-11	80
	12-16	34
	17-65	97
	>65	0
	Unknown	12
	Total	**223**
This table includes cumulative data obtained from 19-Dec-2017 to 23-Jul-2023.		

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

The potential for misuse of this product is extremely low as distribution of product is limited through treatment centers where pharmacists and surgeons have gone through a mandatory educational program.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Retinal deposits, anxiety, dizziness, dellen, choroidal haemorrhage, retinal haemorrhage, rash.

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorized):

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 of the SmPC, Events associated with vitrectomy and anaesthesia: electrocardiogram T wave inversion, eye irritation, eye pain, nausea, vomiting, abdominal pain upper, lip pain, swelling face. endotracheal intubation complication, wound dehiscence.

Known risks that do not impact the risk-benefit profile

- Conjunctival hyperaemia, headache, conjunctival cyst, foreign body sensation in eyes.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks

Increased Intraocular Pressure:

Risk-benefit impact: Increased intraocular pressure is a serious event that could result in the serious outcome of a permanent disability if not prevented or managed quickly.

Retinal tear:

Risk-benefit impact: Retinal tear may lead to retinal detachment which is a serious condition and could result in the serious outcome of a permanent disability if not prevented or managed quickly.

Macular disorders:

Risk-benefit impact: Macular disorders are a group of disorders which could result in the serious outcome of a permanent disability if not prevented or managed quickly.

Cataract:

Risk-benefit impact: Cataracts are serious events that could result in the serious outcome of a permanent disability if not prevented or managed as rapidly as possible.

Intraocular inflammation and/or infection related to the procedure:

Risk-benefit impact: Intraocular inflammation and/or infection could result in the serious outcome of a permanent disability if not prevented or managed appropriately.

Retinal detachment:

Risk-benefit impact: Retinal detachment could lead to the serious outcome of permanent disability if not prevented or managed quickly.

Important Potential Risks

Tumorigenicity:

Risk-benefit impact: As a virus (AAV) is used for delivery of *RPE65* cDNA, the potential for tumorigenicity due to insertional mutagenesis needs to be considered and is an important potential risk based on the seriousness of the outcome of such an event.

Host immune response:

Risk-benefit impact: As a virus (AAV) is used for delivery of *RPE65* cDNA, the potential for host immune response needs to be considered and is an important potential risk based on the likely severity and seriousness of such a reaction.

Third party transmission:

Risk-benefit impact: As a virus (AAV) is used for delivery of *RPE65* cDNA, the potential for third party transmission needs to be considered and is an important potential risk based on the potential for public health impact should this occur.

Missing Information

Long term efficacy (> 4 years):

Risk-benefit impact: Efficacy has been determined up to 4 years with observation ongoing. Due to the nature of the medicinal product, long term efficacy needs to be considered as missing information to ensure that the risk-benefit balance of the product is maintained.

Use in pregnancy and lactation:

Risk-benefit impact: It is unknown whether the safety profile in this patient population will be different to the rest of the population receiving the vector. Biodistribution outside of the eye is limited and was detectable in serum only up to three days post administration. With this limited systemic exposure, AAV infection of the fetus is highly unlikely. However, given the nature of the product there is a need to monitor the safety profile in this patient population.

Use in children < 3 years of age:

Risk-benefit impact: There was concern that the surgical procedure posed a risk in children < 3 years old. Since then however, surgical instruments and technique in paediatric retinal surgery have evolved and the surgical procedure is no longer considered to pose an increased risk in this age group. Retinal cellular proliferation is not complete until 8-12 months and children < 12 months should not receive product due to this as the number of viable retinal cells may be low, impacting on efficacy and therefore impact on the benefit-risk balance of the product.

Long-term safety (> 9 years):

Risk-benefit impact: Safety has been determined up to 9 years. Due to the nature of the medicinal product, long term safety needs to be considered as missing information to ensure that the risk-benefit balance is maintained.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There is no change in safety concerns in this RMP version 3.1.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

Data reported below reflect all related events from the two Phase 1 studies (12 subjects, 23 eyes), and events from the Phase 3 study from the first three years after voretigene administration in the Intervention subjects (20 intervention subjects, 40 eyes), and the first two years after voretigene administration (i.e., after crossover) in the 9 original control subjects (9 control / intervention subjects, 18 eyes). The duration of safety follow-up for these 41 subjects (81 eyes) ranges from at least 2 years up to 11 years following voretigene neparvovec administration.

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important identified risk: vision loss due to progressive chorioretinal atrophy

Important identified risk – vision loss due to progressive chorioretinal atrophy	
Potential mechanisms	Post-injection chorioretinal atrophy, if extending to the fovea centralis, may result in impaired vision. The aetiology of progressive chorioretinal atrophy is unknown.
Evidence source	Cases of progressive chorioretinal atrophy have been described from post-marketing phase and published literature (Gange et al 2021). Events

Important identified risk – vision loss due to progressive chorioretinal atrophy	
	were temporally related to treatment and occurred in the estimated treated area of the bleb site and outside of the bleb area. Retinal atrophy may involve the fovea with possible negative effects on central vision.
Characterization of the risk	Cumulatively until the last PSUR reporting interval, four adverse events describing chorioretinal atrophy were reported in 4 (5%) of 81 eyes in 2 (5%) of 41 subjects in the Spark-sponsored interventional clinical studies for voretigene neparvovec, including the LTFU study. Two eyes of one subject were reported to develop macular degeneration (unusual perifoveal paramacular atrophy), and two eyes of another subject developed injection site atrophy, which was first reported approximately 8 years after treatment. All events were assessed as related to the voretigene neparvovec administration procedure, and two events of macular degeneration were also assessed as related to voretigene neparvovec by the investigator. The two macular atrophy events were associated with a slight decline in visual acuity from baseline, while the other two events of injection site atrophy had improvement in visual acuity compared to baseline. Following reports of chorioretinal atrophy in the post-marketing setting, a retrospective review of fundus photographs available from 38 out of the 41 patients enrolled in the Spark-sponsored interventional clinical studies was performed. In the phase 3 study, chorioretinal atrophy of the macula of treated eyes was found in 15.4% prior to treatment, in 42.6% at Year 1 and in 55.6% after Year 1. In the phase 1 study, chorioretinal atrophy of the macula was present in 35% prior to treatment, in 66.7% at Year 1 and in 73.9% after Year 1. Untreated control eyes showed the following rates of chorioretinal atrophy: 5.9% at baseline and 11.1% at Year 1 in the phase 3 study; 40% at baseline, 42.9% at Year 1 and 41.6% after Year 1 in the phase 1 study. Some of these atrophies involved the fovea. In the phase 3 study, there was involvement of the fovea in 1.9% of treated eyes prior to treatment, as well as at Year 1, and in 5.6% after Year 1. In the phase 1 study, the fovea was involved in 30% of treated eyes prior to treatment, in 38.9% at Year 1 and in 47.8% after Year 1. In the phase 3 study, atrophies in untreated control eyes did not involve the fovea. In the phase 1 study, 40% of atrophies in untreated eyes involved the fovea at baseline, 42.9% at Year 1 and 33.3% after Year 1. Post-injection chorioretinal atrophy (mapped to PTs Chorioretinal disorder, Injection site atrophy, Myopic chorioretinal degeneration, Retinal depigmentation, Retinal degeneration, Retinal dystrophy and Retinal pigment epitheliopathy) has been identified as an adverse drug reaction from post-marketing phase. Events were described as progressive in 10 cases from a US case series published by Gange et al 2021. Although progressive atrophy is a hallmark of patients with LCA, causality with voretigene neparvovec and/or administration procedure was considered as reasonable possibility in these cases based on one or more factors such as correlation with the treated area, plausible time to event onset/detection and causal attribution by the reporting retina specialist or surgeons. From the post-marketing experience, there is evidence from 11 cases reported cumulatively, that the chorioretinal atrophy lesions could extend to the fovea or may be associated with visual impairment. Eight of 11 cases were reported with foveal involvement, although impact on visual acuity varied. Of the 11 cases, the loss in visual acuity (VA) in ETDRS letters was ≥ 15 (or equivalent) in six cases, 10 to 14 (or equivalent) in three cases; in one case, VA decreased by 5 to 9 (or equivalent); in one case, there was foveal involvement without visual impairment. The cumulative post-marketing reporting rate for chorioretinal atrophy related events is 236 events per 1171 treated eyes (20.1%). The cumulative post-marketing reporting rate for visual impairment from the baseline with chorioretinal atrophy is 12 eyes out of 1,171 treated eyes (1.02%) and for

Important identified risk – vision loss due to progressive chorioretinal atrophy	
	foveal involvement with chorioretinal atrophy is 11 eyes out of 1,171 treated eyes (0.9%) until 23-Jul-2023.
Risk factors and risk groups	No risk factors or risk groups have been confirmed.
Preventability	No robust data supporting guidance to treating physicians on specific measures that can be taken to reduce, prevent or manage the risk of chorioretinal atrophy are currently available.
Impact on the risk-benefit balance of the product	Fovea-involving progressive chorioretinal atrophy may cause central visual impairment that may be severe and/or permanent.
Public health impact	Moderate impact

8.3.1.2 Important identified risk: increased intraocular pressure

Important identified risk – increased intraocular pressure	
Potential mechanisms	This is likely related to inflammation as a result of the administration procedure (vitrectomy) and/or response to concomitant steroidal medications that are administered peri-operatively or to treat events of inflammation.
Evidence source	These events have been seen in the clinical trials although not all events were considered related to the administration of the product. In the literature increased intraocular pressure (IOP) is a documented risk with the surgical procedure. Incidence from post-vitrectomy glaucoma studies in the 1970s and 1980s ranges from 20-60%. In a prospective study, approximately 60% of patients had an acute IOP rise of 5-22 mg Hg within 48 hours of pars plana vitrectomy and approximately 36% of patients had an acute IOP rise of > 30 mmHg; with no significant difference between preoperative and late postoperative IOP. In a retrospective cohort study of 111 eyes with a mean follow up of 49 months, there was no long-term increase in IOP following pars plana vitrectomy (Eliassi-Rad 2015). During the post-marketing phase, reports of IOP increase > 30 mmHg requiring treatment with IOP-lowering medication have been reported.
Characterization of the risk	Fourteen AEs of IOP increased were reported in 10 (12%) of the 81 eyes in eight (20%) of 41 subjects in the Spark-sponsored interventional clinical studies including the LTFU study. Of these, 8 events in 8 eyes were assessed as related to the subretinal administration procedure. Among the related AEs, all were mild in severity and all resolved without sequelae. The risk is related to the administration procedure which is not unique to the product. All related events were non-serious. One subject in the 102 study experienced a related AE of increased IOP shortly after the procedure, which resolved. The subject subsequently experienced endophthalmitis, treated with intravitreal antibiotics and local corticosteroids (including depo injection). The subject then developed sustained increased IOP, classified as serious, requiring hospitalization and trabeculectomy, and eventually leading to optic atrophy (ongoing). This event was not considered related to the administration procedure or the product but was determined to be a result of the depo-steroid injection (sub-tenon Kenalog®). The cumulative reporting rate for the risk during the post-marketing phase was 154 events (13%) per 1,171 treated eyes cumulatively until 23-Jul-2023.
Risk factors and risk groups	Presence or history of glaucoma or elevated IOP. Complications from administration procedure.

Important identified risk – increased intraocular pressure	
	Raised IOP has also been associated with prolonged topical as well as systemic steroid use (Thomas and Jay 1988).
Preventability	Prevention is through identification of patients who might not be appropriate to receive treatment (e.g. presence of increased IOP or glaucoma), ensuring adherence to administration technique, and minimizing prolonged use of steroid preparations that are not preservative-free, including avoiding those that cannot be rapidly withdrawn or stopped if indicated.
Impact on the risk-benefit balance of the product	Sustained IOP increase can lead to glaucoma and impaired vision, which may be severe and/or permanent.
Public health impact	Minimal impact

8.3.1.3 Important identified risk: retinal tear

Important identified risk – retinal tear	
Potential mechanisms	Insertion of instruments or excessive traction on the vitreous can cause a retinal tear (McCabe 2006).
Evidence source	Iatrogenic tears have been documented as a significant complication of vitrectomy with an incidence of about 5% (McCabe 2006). Another study reported a similar incidence of 6% in 219 eyes undergoing 20-gauge vitrectomy (Scartozzi et al 2007). However, other groups have reported a higher incidence of iatrogenic retinal tears; in a study of 645 eyes undergoing 20gauge vitrectomy, iatrogenic retinal breaks occurred in 15% of eyes intraoperatively, and resulting postoperative retinal detachment occurred in 2% of eyes (Ramkissoon et al 2010). Another study reported postoperative retinal detachment in 4% of 173 eyes undergoing 20-gauge vitrectomy for epiretinal membrane (Grewing and Mester 1996).
Characterization of the risk	Four of 81 (5%) eyes in 4/41 (10%) subjects administered voretigene neparvovec in the Spark-sponsored interventional clinical studies including the LTFU study had a retinal tear. Retinal tears were observed and repaired by the surgeon with laser pexy during the vector administration procedures in one Phase 1 subject and three Phase 3 subjects. All events were considered related to the procedure and none were considered related to the product. All events were non-serious and resolved without sequelae. Three events were mild in intensity and one was moderate. The risk is associated with the administration procedure, both the vitrectomy and the subretinal injection. The cumulative reporting rate for the risk during the post-marketing phase was 16 events (1.3%) per 1.171 treated eyes cumulatively until 23-Jul-2023.
Risk factors and risk groups	These events are usually spontaneous and cannot be predicted. Risk factors include myopia, lattice degeneration, previous eye surgery and trauma. Complications from administration procedure.
Preventability	Adherence to administration procedure is important in reducing the risk of this event. Surgeon awareness of the potential risk is important to identify retinal tears during or after the administration procedure and to treat as clinically indicated when identified.
Impact on the risk-benefit balance of the product	Retinal tears can lead to retinal detachment which can lead to visual impairment that may be severe and/or permanent.

Important identified risk – retinal tear	
Public health impact	Minimal impact

8.3.1.4 Important identified risk: macular disorders

Important identified risk – macular disorders	
Potential mechanisms	These macular disorders may be related to the administration procedure: due to vitrectomy with associated traction and/or due to subretinal injection which may cause tissue expansion (mechanical stress) due to increased pressure in the subretinal space.
Evidence source	These events have been seen in clinical trials. In the literature idiopathic macular holes occur at an age and sex adjusted incidence of 7.8 persons and 8.69 eyes per 100,000 population per year in Olmsted County, Minnesota (Jacobson et al 2012). Of 45 patients undergoing pars plana vitrectomy for idiopathic epiretinal membrane, one patient (2%) developed macular hole six months postoperatively (Ibarra et al 2005). Epiretinal membrane development after vitrectomy has been reported; of 312 consecutive eyes that underwent pars plana vitrectomy for primary rhegmatogenous retinal detachment, 28 (9%) developed epiretinal membrane during the postoperative period (Martinez-Castillo et al 2012). In another series of 141 patients undergoing pars plana vitrectomy for retinal detachment, 18 (13%) were noted to have a postoperative epiretinal membrane at clinical examination (Katira et al 2008). In another program where AAV vector was delivered to the subretinal space, foveal thinning was reported following subfoveal injections in two out of five subjects receiving central macular injections, without loss of visual function (McCannel et al 2009). During the Spark-sponsored clinical program, one noteworthy case has been reported cumulatively. In this case, the patient had macular thinning with resultant permanent loss of foveal function (at one year follow-up visual acuity was 20/320 and full-field stimulus threshold was one decibel) in right eye.
Characterization of the risk	Eleven (14%) of 81 eyes administered voretigene neparvovec in 8 (20%) of 41 subjects in the Spark-sponsored interventional clinical studies including the LTFU study developed events grouped as macular disorders (mapped to PT Eye disorder [foveal dehiscence], Epiretinal membrane, Macular hole, Macular degeneration [macular thinning; unusual perifoveal perimacular atrophy], Maculopathy [macular pucker], and Retinal foveal disorder [foveal thinning and loss of foveal function]). Of these, 13 events in 11 eyes were assessed as related to the subretinal administration procedure, and 2 newly reported events of macular degeneration (unusual perifoveal perimacular atrophy) in both eyes of 1 participant were also assessed as related to voretigene neparvovec. The cumulative reporting rate for the risk during the post-marketing phase was 57 events (4.9%) per 1,171 treated eyes cumulatively until 23-Jul-2023.
Risk factors and risk groups	Risks include underlying retinal disorder, aging and vitreomacular traction. Complications from administration procedure.
Preventability	Adherence to administration procedure technique is important in minimizing the risk of these events, including the recommended site of injection of at least 2 mm distal to the center of the fovea.
Impact on the risk-benefit balance of the product	These macular disorders may cause visual impairment that may be severe and/or permanent.

Important identified risk – macular disorders	
Public health impact	Minimal impact

8.3.1.5 Important identified risk: cataract

Important identified risk – cataract	
Potential mechanisms	Vitrectomy may lead to cataract formation as a result of disturbance of oxygen balance or possible mechanical trauma to the lens. Cataract may be a secondary effect due to other ocular events and/or due to the underlying disease (McCabe 2006). Acute cataract formation may also be due to direct trauma to the lens by surgical instruments during the procedure.
Evidence source	These events have been seen in clinical trials. In the literature the prevalence of cataract has been noted to be 1 in 49 or 2.02% in the US and incidence has been noted to be 1 in 679 or 0.15% in the US in the general population. Patients with hereditary retinal degeneration have a higher incidence of cataract formation. The prevalence of posterior subcapsular lens opacities or bilaterally aphakia was 53% (180/338) with mean age of 38.7 years (Fishman et al 1985). In a study describing the natural history of retinal degenerative disease in individuals with autosomal recessive mutations in the *RPE65* gene, cataracts or other lens opacities were seen in at least one eye in 14 (20.0%) subjects; 11 (78.5%) had bilateral lens abnormalities, 2 subjects had lens abnormalities in only the right eye and one subject had a lens abnormality in only the left eye. The mean age of subjects at the time of first lens abnormality was 26 years of age (Spark 2017). In 142 eyes of 89 patients with retinitis pigmentosa, 100 eyes showed posterior subcapsular lens opacity (Jackson et al 2001). Post vitrectomy nuclear sclerotic cataract progression was seen in 60/74 (81%) eyes compared to 13/74 (18%) in the control group at 6 months and at 2 years 100% of the vitrectomy eyes had progression compared to 8% of controls (Cheng et al 2001). A retrospective review by Cherfan et al showed 80/100 eyes post vitrectomy for idiopathic macular pucker developed visually significant nuclear sclerotic cataract or had undergone cataract extraction compared to 24/100 in the control group (Cherfan et al 1991). During the post-marketing phase none of the cases associated with cataract led to severe or permanent visual impairment.
Characterization of the risk	Cataract was reported in 23 (28%) of 81 eyes in 14 (34%) of 41 subjects in the Spark-sponsored interventional clinical studies including the LTFU study. Of these, 21 events in 20 eyes were assessed as related to the subretinal administration procedure. All events were non-serious. Elective cataract extraction procedures have been performed for some of the events. Overall, there are 9 eyes in 6 subjects with ongoing events of cataract. All events were mild or moderate. Risk is related to the administration procedure and the underlying disease. The cumulative reporting rate for the risk during the post-marketing phase was 88 events (7.5%) per 1,171 treated eyes cumulatively until 23-Jul-2023.
Risk factors and risk groups	Risks include aging, trauma, and vitrectomy procedure. Also associated with inherited retinal disease.
Preventability	Adherence to administration procedure technique is important in reducing the risk of this event.
Impact on the risk-benefit balance of the product	Cataracts may cause visual impairment that may be severe and/or may require surgical intervention for resolution.

Important identified risk – cataract	
Public health impact	Minimal impact

8.3.1.6 Important identified risk: intraocular inflammation and/or infection related to the procedure

Important identified risk – intraocular inflammation and/or infection related to the procedure	
Potential mechanisms	May be related to the adeno-associated viral vector or the administration procedure, including the vitrectomy, subretinal injection, and fluid-air exchange.
Evidence source	These events have been seen in the clinical trials and were considered related to the procedure. In the literature, it is noted that endophthalmitis can occur after vitrectomy for any cause, but it is rare. In a systematic review of endophthalmitis after vitrectomy, the overall rate of endophthalmitis with 20-gauge vitrectomy was 3 cases per 10,000 procedures (Govetto et al 2013). The incidence of endophthalmitis post pars plana vitrectomy has been reported to be between 0.03% and 0.07% (Pandya 2016). The rate of endophthalmitis after secondary intraocular lens implantation was 0.2% (Pandya 2016). During the post-marketing phase, serious cases of intraocular inflammation associated with visual impairment have been reported cumulatively.
Characterization of the risk	Five (6%) of 81 eyes in 3 (7%) of 41 subjects in the Spark-sponsored interventional clinical studies including the LTFU study for voretigene neparvovec reported events grouped as intraocular inflammation and/or infection (mapped to PT Eye inflammation). These seven events in five eyes were assessed as related to the subretinal administration procedure. None of the events were assessed as related to voretigene neparvovec. All events were non-serious and resolved without sequelae. All events were mild or moderate in severity. Risk is related to the administration procedure. The cumulative reporting rate for the risk during the post-marketing phase was 157 events (13.4%) per 1,171 treated eyes cumulatively until 23-Jul-2023. Of note, the majority of cases reported more than one term related to intraocular inflammation or symptoms, and these 88 events were reported in 42 cases.
Risk factors and risk groups	Complications from administration procedure.
Preventability	Adherence to administration procedure technique and perioperative management are important in minimizing the risk. Use of standards of eye care treatment such as topical steroids and antibiotics to the eyes. The individual administration procedure to each eye performed on separate days and single use vials are expected to minimize the risk.
Impact on the risk-benefit balance of the product	Intraocular inflammation and/or endophthalmitis may cause visual impairment that may be severe and/or permanent.
Public health impact	Minimal impact

8.3.1.7 Important identified risk: retinal detachment

Important identified risk – retinal detachment	
Potential mechanisms	Retinal detachments can be caused by a retinal tear.
Evidence source	Retinal tear and detachment are well- known complications of vitrectomy surgery. Rhegmatogenous retinal detachment is the most common type of retinal detachment and develops when a tear in the retina causes fluid accumulation, resulting in the separation of retinal layers from the underlying RPE. There is very sparse literature on vitrectomy complications in pediatric patients undergoing vitrectomy for indications other than retinopathy of prematurity-associated retinal detachment., It is well known that separation of the pediatric hyaloid from the retina is challenging; consequently, late post-operative retinal tear and detachment can develop from residual vitreous base contracture occurring late in the post-operative period. The literature in adult eyes undergoing vitrectomy provides some insights into the prevalence and timing of post-operative retinal tear and detachment. For example, in a study of 645 eyes undergoing 20-gauge vitrectomy (as used in the Phase 3 clinical trial program), iatrogenic retinal breaks occurred in 15.2% of eyes intraoperatively, and resulting postoperative retinal detachment occurred 1.7% of eyes at a median of 7.5 weeks (range 3-40 weeks) (Ramkissoon et al 2010). Another study reported postoperative retinal detachment in 4% of 173 eyes undergoing 20-gauge vitrectomy for epiretinal membrane, with a mean time to presentation at 3.75 months after vitrectomy (Grewing and Mester 1996). Regarding the procedure and instrumentation, there have been significant changes since 2013, when the Phase 3 protocol was written. Small-gauge vitrectomy probes have decreased in diameter from 20-gauge to 23-gauge, to 25- and 27-gauge, with self-sealing wounds that no longer require suture closure. Instead of traditional incisions through which instruments are repeatedly introduced into the eye, trocar systems now protect the vitreous base during small gauge instrument insertion, facilitating less traumatic entry and limiting inadvertent vitreous traction, which potentially decreases the risk of secondary retinal tear and subsequent retinal detachment. Valved trocars are now commonplace, preventing egress of infusion solution intraoperatively, which further limits vitreous incarceration, traction and retinal tear; valved trochars also facilitate better control of intraocular pressure and fluidics during surgery, which potentially decreases the risk of intraoperative hemorrhage and/or choroidal detachment. According to the American Society of Retina Specialists Preference and Trends Survey, over 75% of global retina specialists use valved trocars in 76-100% of cases in 2017, compared to less than 25% of retina specialists in 2013. In addition, recent technology enables modulation of vacuum and duty cycle (closed port instead of open port bias), as well as high speed cutting (up to 7500/minute), at the vitreous base to minimize vitreous traction, and potentially decrease the risk of retinal tear and detachment. Furthermore, new wide-angle intraocular viewing systems and powerful light sources based on Xenon technology have evolved, providing better viewing and illumination respectively. The literature supports that smaller-gauge vitrectomy with the use of trochars may yield fewer complications, particularly retinal tear and detachment. In contrast to the greater incidence of retinal tear and detachment with 20-guage vitrectomy as cited above, in a consecutive series of 92 eyes undergoing 23-gauge vitrectomy, intraoperative retinal tears were observed in 2.2% of eyes (Gupta 2008). In several other studies of small-gauge vitrectomy surgery, no intraoperative tears were noted (77 eyes, 23-gauge vitrectomy, Fine 2007; 45 eyes, 25-gauge vitrectomy, Ibarra et al 2005; 140 eyes, 25-gauge vitrectomy, Lakhanpal 2005; 95 eyes, 27-gauge vitrectomy, Kahn 2015). In one study comparing 20-gauge vitrectomy to 25-gauge vitrectomy for the treatment of macular disease, 14 (6.4%) of 219 eyes in the 20-gauge group

Important identified risk – retinal detachment	
	had sclerotomy-related retinal breaks versus 4 (3.1%) of 128 eyes in the 25-gauge group, although this trend was not statistically significant (Fisher exact test, P- value 0.22) (Scartozzi et al 2007). Consequently, given the anticipated use of smaller gauge vitrectomy instrumentation, including the trochars, and subretinal cannulas, the safety of the procedure is likely enhanced as discussed above.
Characterization of the risk	Two (2.5%) of 81 eyes in two (5%) of 41 subjects administered voretigene neparvovec in the Spark-sponsored interventional clinical studies including the LTFU study had a retinal detachment. Both events (one per subject) were assessed as related to the subretinal administration procedure. One of these events described a tractional (potentially rhegmatogenous) detachment, and the other described a peripheral detachment of unconfirmed etiology. Cases of retinal detachment with reasonable temporal relationship to Luxturna administration and requiring surgical correction have been reported in the long-term follow-up study AAV2-hRPE65v2-LTFU-01, as well as post-marketing surveillance. In one case, the event was reported in conjunction with a macular hole associated with transient loss of vision (VA reduced to hand motion) The cumulative reporting rate for the risk during the post-marketing phase was 14 events (1.2%) per 1,171 treated eyes cumulatively until 23-Jul-2023.
Risk factors and risk groups	These events are usually spontaneous and can't be predicted. Myopia, lattice degeneration, pars plana vitrectomy, trauma, and family history are risk factors for retinal detachment.
Preventability	Adherence to the administration procedure is important in reducing the risk of this event. Surgeon awareness of the potential risks related to the administration procedure is important to identify retinal tears during or after the administration procedure and to treat as clinically indicated when identified.
Impact on the risk-benefit balance of the product	Retinal detachment may cause visual impairment that may be severe and/or permanent.
Public health impact	Minimal impact

8.3.1.8 Important potential risk: tumorigenicity

Important potential risk – tumorigenicity	
Potential mechanisms	Insertional mutagenesis
Evidence source	This is an advanced therapeutic medicinal product (ATMP) specific risk consideration.
Characterization of the risk	Two serious events (one of each) of colon tubular adenoma (one in 41 patients, 2%) and acute myeloid leukemia (one in 41 patients, 2%), as well as five non-serious events of pyogenic granuloma, haemangioma, meningioma benign, oral fibroma, and oral papilloma have been reported in a total six subjects treated with voretigene neparvovec in Spark-sponsored interventional clinical studies including the LTFU study. These events were considered by the investigator as unrelated to the drug. and administration procedure. Acute

Important potential risk – tumorigenicity	
	myeloid leukemia resulted in a fatal outcome, while 4 events recovered without sequelae and the remaining two are ongoing. Two post-marketing events of tumorigenicity have been reported cumulatively until 23-Jul-2023. The cumulative number of events are too low to draw any meaningful conclusions on the post-marketing reporting rate.
Risk factors and risk groups	Unknown
Preventability	Unknown
Impact on the risk-benefit balance of the product	May be life-threatening
Public health impact	Minimal impact

8.3.1.9 Important potential risk: host immune response

Important potential risk – host immune response	
Potential mechanisms	Related to host response/immune reaction to either vector capsid (AAV2) or transgene product (RPE65) (Anand et al 2002; Daya and Berns 2008).
Evidence source	Intraocular inflammation or immune responses following gene therapy with a recombinant AAV2/2 vector carrying the RPE65 cDNA (1E12 vg) has been described in literature (Bainbridge et al 2008; Bainbridge et al 2015). No clinically significant inflammatory response to the investigational product has been observed and no dose-limiting toxicity was seen in the Spark-sponsored interventional clinical studies including the LTFU study. During the post-marketing phase, no cases of suspected or confirmed host immune response have been reported.
Characterization of the risk	Could lead to a significant inflammatory reaction, however there were no clinically significant cytotoxic T-cell responses to either vector capsid (adeno-associated viral vector serotype 2 [AAV2]) or transgene product (RPE65) in any of the subjects from Spark's sponsored interventional clinical studies including the LTFU study and there has been no inflammatory response, other than occasional transient mild redness and inflammation of the eye (a known common occurrence after ocular procedures), which was not specific to voretigene neparvovec. At all doses of voretigene neparvovec evaluated in studies AAV2-hRPE65v2-101 and AAV2-hRPE65v2-301, intraocular inflammation or immune responses were mild in severity and extra-ocular exposure was limited. No post-marketing events have been reported cumulatively until 23-Jul-2023.
Risk factors and risk groups	Unknown
Preventability	Use of standards of immunomodulatory and eye care treatments such as oral and topical ocular steroids. Administration to each eye performed on separate days within a close interval, but no fewer than 6 days apart.
Impact on the risk-benefit balance of the product	Unknown
Public health impact	Minimal impact

8.3.1.10 Important potential risk: third party transmission

Important potential risk – third party transmission	
Potential mechanisms	Direct exposure from handling, preparing or administering the product and waste materials, or from shedding of the product after administration.
Evidence source	This is an ATMP specific risk consideration – Environmental Risk Assessment. Transient and low levels of vector DNA were detected in tears and occasionally in serum samples from overall 14 of 29 (48%) Phase 3 subjects. However, there were no instances of third party transmission noted during the clinical development of voretigene neparvovec. During the post-marketing phase, no cases of suspected or confirmed third party transmission have been reported.
Characterization of the risk	No instances of third party transmission have been reported during the clinical development of voretigene neparvovec. In order to assess the risk of third party transmission the presence of viral vectors in tears and serum of clinical trial participants was monitored during clinical development. In 13 of 29 (45%) subjects in the Phase 3 study, voretigene neparvovec vector DNA sequences were detected in tear samples. Vector DNA sequences were detected in the serum in three of 29 (10%) subjects, including two subjects with positive tear samples, up to Day 3 following each injection. No post-marketing events have been reported cumulatively until 23-Jul-2023.
Risk factors and risk groups	Healthcare workers, caregivers or other close contacts of the treated individual (partners and family members) including pregnant women and immunosuppressed individuals are particularly at risk of third-party transmission.
Preventability	Training and instructions for safe handling and disposal of affected materials for 14 days following product administration. For pharmacy personnel, use of personal protective equipment during the preparation of Luxturna. Exclusion from donation of blood, organs, tissues, and cells for transplantation after product administration.
Impact on the risk-benefit balance of the product	Unknown
Public health impact	Minimal impact

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

8.3.2.1 Missing information: long-term efficacy (> 4 years)

Missing information – long-term efficacy (> 4 years)	
Evidence source	ATMP specific consideration
Anticipated risk/consequence of the missing information	Although not anticipated, lack of efficacy may occur long term. Patients receiving the product more than 3 years ago should be assessed to further characterize this risk.

8.3.2.2 Missing information: use in pregnancy and lactation

Missing information – use in pregnancy and lactation	
Evidence source	Literature

Missing information – use in pregnancy and lactation	
Population in need of further characterization	Pregnant patients and those lactating to further characterize any specific risks in this patient population.

8.3.2.3 Missing information: use in children < 3 years of age

Missing information – use in children < 3 years of age	
Evidence source	Literature
Population in need of further characterization	Children < 3 years old to further characterize any specific risks in this patient population.

8.3.2.4 Missing information: long-term safety (> 9 years)

Missing information – long-term safety (> 9 years)	
Evidence source	ATMP specific consideration.
Anticipated risk/consequence of the missing information	Although not anticipated, long-term safety issues may occur. Patients receiving the product more than 9 years ago should be assessed to further characterize this risk.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

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

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below (the targeted follow-up checklist is provided in Annex 4):

Important identified risk: Vision loss due to progressive chorioretinal atrophy

- (Retinal) atrophy at injection site and/or progression of atrophy

10.2 Part III.2. Additional pharmacovigilance activities

Summary of global registry study CLTW888A12401 (ex-US): Category 1 EU PASS

Study title: a post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US)

Rationale and study objectives: The objective of this registry-based study is to collect long-term safety information (i.e., for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Study design: Study CLTW888A12401 (previously referred to as SPKRPE-EUPASS) is a post-authorization, multicenter, multinational, longitudinal, observational safety registry study.

Study population: All patients receiving voretigene neparvovec. This includes patients with either LCA or RP due to biallelic *RPE65* mutations so that both diseases can be assessed.

A standardized questionnaire is used that includes a checklist for

- ADRs of special interest
- Local AEs
- General side effects
- Lack of efficacy and/or decline in efficacy over time
- Patients/caregivers assessments

Milestones: Annual progress reports, 5-year follow-up, study finish and final report.

Summary of long-term follow-up study AAV-hRPE65v2-LTFU-01 (in US): Category 1 EU PASS

Long-term follow-up (LTFU) study for participants in the clinical program (conducted in the US).

Rationale and study objectives: Study AAV2-hRPE65v2-LTFU-01 is a long-term safety and efficacy follow-up study of trial participants who received voretigene neparvovec in the clinical program.

Study design: Open-label, follow-up study.

Study population: Trial participants who received voretigene neparvovec in the clinical program.

Milestones: LTFU annual progress reports, 15-year follow-up (last patient last visit 2030), study finish and final report.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
CLTW888A12401 (previously referred to as SPKRPE-EUPASS) A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) Ongoing	The objective of this registry-based study is to collect long-term safety information (i.e., for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.	Vision loss due to progressive chorioretinal atrophy Increased IOP Retinal tear Macular disorders Cataract Intraocular inflammation and/or infection related to the procedure Retinal detachment Tumorigenicity Host immune response Third party transmission Lack of efficacy and/or decline in the efficacy over time Use in pregnancy and lactation Use in patients < 3 years of age	Annual progress reports	Annually
			Final report	30-Jun-2030
LTFU-01 A long-term follow-up study in subjects who received an AAV2-hRPE65v2 administered via subretinal injection (conducted in the US) Ongoing	Study AAV2-hRPE65v2-LTFU-01 is a long-term safety and efficacy follow-up study of trial participants who received voretigene neparvovec in the clinical program.	Increased IOP Retinal tear Macular disorders Cataract Intraocular inflammation and/or infection related to the procedure Retinal detachment Tumorigenicity Host immune response Use in pregnancy and lactation Long-term efficacy (> 4 years) Long-term safety (> 9 years)	LTFU annual progress reports	Annually
			15-year follow-up (last patient last visit)	2030
			Study finish and final report	2031
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

11 Part IV: Plans for post-authorization efficacy studies

Long-term efficacy data will be collected through continuing follow-up of the current clinical cohort (LTFU-01) and through collection of data from the registry study (CLTW888A12401).

The 41 subjects who received voretigene neparvovec in the US clinical program have been enrolled in a long-term follow-up (LTFU) protocol, AAV2-hRPE65v2-LTFU-01 (EU PASS category 1), in which they will be followed for 15 years post vector administration. This LTFU protocol seeks to characterize clinical outcomes following the voretigene neparvovec gene transfer, with assessments including annual history, physical and ophthalmic examinations, blood tests, urinalysis, and retinal/visual function tests. Adverse event reporting focuses on adverse events related to the prior administration of voretigene neparvovec and the development of oncologic, hematologic, neurologic, and auto-immune events.

In the registry study CLTW888A12401 (ex-US; EU PASS category 1) ophthalmological examination data will also be collected. This includes visual acuity, visual fields, full-field light sensitivity threshold testing, and optical coherence tomography imaging.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Vision loss due to progressive chorioretinal atrophy	Routine risk minimization: 1.SmPC section 4.8 2.PL section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Increased intraocular pressure	Routine risk minimization: 1. SmPC section 4.4 and 4.8. 2. PL section 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: 1. SmPC section 4.4 contains a recommendation for patients to avoid air travel or other travel to high elevations until the air bubble formed as a result of Luxturna administration has dissipated from the eye. This should be verified by an ophthalmic examination. 2. PL section 2 contains the same advice. Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Retinal tear	Routine risk minimization: 1. SmPC section 4.4 and 4.8. 2. PL section 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: 1. The PL states that the patient should seek immediate care from your doctor if you see flashes or floaters in your vision, or if you notice any worsening or blurred vision. Other routine risk minimization measures beyond the Product Information: Prescription only product
Macular disorders	Routine risk minimization: 1. SmPC section 4.4 and 4.8. 2. PL section 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: 1. SmPC section 4.4 states to not administer Luxturna in the immediate vicinity of the fovea.

Safety concern	Routine risk minimization activities
	2. The PL states that the patient should inform the doctor about any visual disturbances and light sensitivity. Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Cataract	Routine risk minimization: 1. SmPC section 4.8. 2. PL section 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: 1. The PL states that the patient should inform the doctor about any visual disturbances, light sensitivity, or blurred vision. Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Intraocular inflammation and/or infection related to the procedure	Routine risk minimization: 1. SmPC section 4.2, 4.3, 4.4 and 4.8. 2. PL section 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: 1. SmPC section 4.2 provides guidance regarding aseptic techniques and use of topical microbicide. 2. SmPC section 4.4 states to inform the patient to report any symptoms suggestive of endophthalmitis without delay 3. SmPC section 4.4 states to inform the patient to avoid swimming. 4. The PL states that the patient should seek immediate care from your doctor if your eye or eyes become red, painful, sensitive to light, you see flashes or floaters in your vision, or if you notice any worsening or blurred vision, and to inform the doctor about any visual disturbances and light sensitivity and that they should avoid swimming until they have spoken to their doctor. Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Retinal detachment	Routine risk minimization: 1. SmPC section 4.2 and 4.4. 2. PL section 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: 1. SmPC section 4.4 states to inform the patient to report any symptoms suggestive of retinal detachment without delay. 2. The PL states that the patient should seek immediate care from your doctor if you see flashes or floaters in your vision, or if you notice any worsening or blurred vision. Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Tumorigenicity	Routine risk minimization: None Routine risk minimization activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimization activities
	None Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Host immune response	Routine risk minimization: 1. SmPC section 4.2. 2. PL section 3. Routine risk minimization activities recommending specific clinical measures to address the risk: 1. SmPC section 4.2 provides an immunomodulatory regime to be used peri-operatively. 2. The PL states that an immunomodulatory regime will be used and not to stop taking the medication without talking to the doctor. Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Third party transmission	Routine risk minimization: 1. SmPC section 4.4, 5.2, and 6.6. 2. PL section 2. Routine risk minimization activities recommending specific clinical measures to address the risk: 1. SmPC section 4.4 provides advice on personal protective equipment and how to handle waste material from dressings, tears and nasal secretions. An exclusion from donation of blood, organs, tissues, and cells for transplantation is also included. 2. SmPC section 6.6 provides instructions for preparation of product and what to do in the event of accidental exposure 3. The PL provides advice on personal protective equipment and disposal of dressings and waste materials. An exclusion from donation of blood, organs, tissues, and cells for transplantation treatment is also included. Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Long-term efficacy (> 4 years)	Routine risk minimization: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Use in pregnancy and lactation	Routine risk minimization: 1. SmPC section 4.6. 2. PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information:

Safety concern	Routine risk minimization activities
	1. Prescription only product
Use in children < 3 years of age	Routine risk minimization: 1. SmPC section 4.2. 2. PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: 1. Prescription only product
Long-term safety (> 9 years)	Routine risk minimization: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: 1. Prescription only product

12.2 Part V.2. Additional Risk minimization measures

Additional risk minimization measure 1: Distribution through treatment centers who have participated in the mandatory educational program on use of product and pharmacy training.

Study sites/treatment centers should fulfil the following three criteria: (1) the presence of a specialist ophthalmologist with expertise in care and treatment of patients with IRDs. (2) the presence of or affiliation with a retinal surgeon experienced in subretinal surgery and capable of administrating voretigene neparvovec, (3) the presence of a clinical pharmacy capable of handling and preparing AAV vector-based gene therapy products.

Objectives:

The objectives of the additional risk minimization measure are to ensure correct use of the product through treatment centers and pharmacies that have participated in the mandatory educational program so as to minimize the risks associated with product administration. The risks to be addressed are those associated with the administration procedure including increased intraocular pressure, retinal tear, macular disorders, cataract, intraocular inflammation and/or infection related to the procedure and retinal detachment.

Rationale for the additional risk minimization activity:

The important identified risks are related to the administration of voretigene neparvovec. Limiting the use of product through treatment centers and pharmacies who have participated in the mandatory educational program will ensure that the product will be administered by appropriately qualified and trained health care professionals who are aware of the risks and precautions that are needed.

Target audience and planned distribution path:

Vitreoretinal surgeons and pharmacists in the treatment centers.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Assessment of the frequency and nature of reports of intraocular pressure, retinal tear, macular disorders, cataract, intraocular inflammation and/or infection related to the procedure and retinal detachment through registry data and spontaneous reporting.

Additional risk minimization measure 2: Patient alert card.

Objectives:

The card will highlight the importance of the patient attending follow-up visits and reporting side effects to the patient's physician. The card will also serve as information for other healthcare professionals that may treat the patient to inform them that the patient has undergone gene therapy, and the importance of reporting adverse events. Contact information for adverse event reporting will be included. The patient card will also be available in large print and as an audio file.

To inform other healthcare professionals of the patient's treatment with gene therapy.

Rationale for the additional risk minimization activity:

The card will ensure the patient/carer is aware of the importance of reporting side effects/adverse events to the patient's physician. A reminder of the importance of compliance with follow-up will ensure that the patient is seen regularly by the health care professional so that important side effects can be diagnosed and treated promptly.

The card will also serve as information for other health care professionals that may treat the patient to inform them that the patient has undergone gene therapy.

Target audience and planned distribution path:

Patients and caregivers.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Assessment of the frequency and nature of reports of intraocular pressure, retinal tear, macular disorders, cataract, intraocular inflammation and/or infection related to the procedure and retinal detachment through registry data and spontaneous reporting.

Removal of additional risk minimization activities:

Not applicable.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Vision loss due to progressive chorioretinal atrophy	Routine risk minimization measures: • SmPC section 4.8 • PL section 4 Other routine risk minimization measures beyond the Product	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up checklist Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Information:Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card	A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401)
Increased intraocular pressure	Routine risk minimization measures: • SmPC section 4.4 and 4.8 • PL section 2 and 4 Recommendation for patients to avoid air travel or other travel to high elevations until the air bubble formed as a result of Luxturna administration has dissipated from the eye, which should be verified by an ophthalmic examination in SmPC section 4.4 and PL section 2 Other routine risk minimization measures beyond the Product Information: Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)
Retinal tear	Routine risk minimization measures: • SmPC section 4.4 and 4.8 • PL section 2 and 4 PL section 2 contains advice for patients regarding which symptoms they should contact the doctor for Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Macular disorders	Routine risk minimization measures: • SmPC section 4.4 and 4.8 Advice in SmPC section 4.4 on where Luxturna should not be administered • PL section 2 and 4 PL section 2 contains advice for patients regarding which symptoms they should contact the doctor for Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)
Cataract	Routine risk minimization measures: • SmPC section 4.8 • PL section 2 and 4 PL section 2 contains advice for patients regarding which symptoms they should contact the doctor forOther routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)
Intraocular inflammation and/or infection related to the procedure	Routine risk minimization measures: • SmPC section 4.2, 4.3, 4.4 and 4.8 Guidance regarding aseptic technique and use of topical microbicide in SmPC section 4.2. States what symptoms the patients need to be informed to report without delay in section 4.4. • PL section 2 and 4 PL section 2 contains advice for patients regarding which symptoms they should contact the doctor for	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (LTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Avoidance of swimming in SmPC section 4.4 and PL section 2. Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card	
Retinal detachment	Routine risk minimization measures: • SmPC section 4.2 and 4.4 States what symptoms the patients need to be informed to report without delay in section 4.4. • PL section 2 and 4 PL section 2 contains advice for patients regarding which symptoms they should contact the doctor for Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)
Tumorigenicity	Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Host immune response	Routine risk minimization measures: • SmPC section 4.2 • PL section 3 The immunomodulatory regime to be used is stated in the SmPC section 4.2 and referenced PL section 3. Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)
Third party transmission	Routine risk minimization measures: • SmPC section 4.4, 5.2 and 6.6 Advice on how to handle waste material from dressings, tears and nasal secretions and on personal protective equipment in section 4.4. An exclusion from donation of blood, organs, tissues, and cells for transplantation is included. Advice on managing accidental exposure is in section 6.6. • PL section 2 PL section 2 provides advice on personal protective equipment and disposal of dressings and waste materials. An exclusion from donation of blood, organs, tissues, and cells for transplantation is included. Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401)
Long-term efficacy (> 4 years)	Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401)

Safety concern	Risk minimization measures	Pharmacovigilance activities
		• Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)
Use in pregnancy and lactation	Routine risk minimization measures: • SmPC section 4.6 • PL section 2 • Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)
Use in children < 3 years of age	Routine risk minimization measures: • SmPC section 4.2 • PL section 2 Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401)
Long-term safety (> 9 years)	Other routine risk minimization measures beyond the Product Information: • Prescription only product Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)

13 Part VI: Summary of the risk management plan for Luxturna (voretigene neparvovec)

This is a summary of the risk management plan (RMP) for voretigene neparvovec. The RMP details important risks of Luxturna, how these risks can be minimized, and how more information will be obtained about Luxturna's risks and uncertainties (missing information).

Luxturna's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Luxturna should be used.

This summary of the RMP for Luxturna should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Luxturna's RMP.

13.1 Part VI: I. The medicine and what it is used for

Luxturna is authorised 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. (see SmPC for the full indication). It contains voretigene neparvovec as the active substance and it is given by subretinal injection.

Biallelic mutations in the *RPE65* gene lead to inherited disease causing ongoing deterioration of the retina. The gene mutation leads to decreased or lack of the activity of the enzyme retinoid isomerohydrolase which is encoded by *RPE65* gene and eventually leads to the accumulation of toxic precursors and reduced functioning of the cells in the retina. The pattern of inheritance is autosomal recessive i.e. both parents are carriers or have one defective copy of the gene. Leber congenital amaurosis (LCA) is estimated to affect ~1/81,000 of individuals. 8-16% of these patients are identified as having mutations in the *RPE65* gene. The condition can affect both children and adults, both male and female and the first signs of the condition can appear as soon as 2-3 months of age. The condition is usually diagnosed within the first few months of life and leads to severe visual impairment, abnormal eye movements (nystagmus) and will progress to total blindness.

Some patients with autosomal recessive *RPE65* gene mutations may have been diagnosed with retinitis pigmentosa, which has a more variable age of onset and extent of vision loss than LCA. Retinitis pigmentosa (RP) is estimated to affect approximately 1/3,500 to 1/4,000 individuals. It is estimated that a range of 1 to 3% of all patients with RP have underlying genetic mutations in the *RPE65* gene. The condition can affect both children and adults, both male and female. The condition has a more variable age of onset than LCA but similarly leads to severe visual impairment, abnormal eye movements (nystagmus) and will progress to total blindness. There are no other pharmacological treatments approved for *RPE65* mutation-associated inherited retinal disease.

Further information about the evaluation of Luxturna's benefits can be found in Luxturna's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage*:* https://www.ema.europa.eu/en/medicines/human/EPAR/luxturna.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Luxturna, together with measures to minimize such risks and the proposed studies for learning more about Luxturna's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Luxturna, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Luxturna is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of Luxturna are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Luxturna. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

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

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important identified risk: Vision loss due to progressive chorioretinal atrophy

Evidence for linking the risk to the medicine	Cases of progressive chorioretinal atrophy have been described from post marketing phase and published literature. Events were temporally related to treatment and occurred in the estimated treated area of the bleb site and outside the bleb area. Retinal atrophy may involve the fovea with possible negative effects on central vision. Cumulatively until the last PSUR reporting interval, four adverse events describing chorioretinal atrophy were reported in 4 (5%) of 81 eyes in 2 (5%) of 41 subjects in the Spark-sponsored interventional clinical studies for voretigene neparvovec, including the LTFU study. From the post-marketing experience, there is evidence from 11 cases reported cumulatively, that the chorioretinal atrophy lesions could extend to the fovea or may be associated with visual impairment. Eight of 11 cases were reported with foveal involvement, although impact on visual acuity varied. Of the 11 cases, the loss in visual acuity (VA) in ETDRS letters was ≥ 15 (or equivalent) in six cases, 10 to 14 (or equivalent) in three cases; in one case, VA decreased by 5 to 9 (or equivalent); in one case, there was foveal involvement without visual impairment. Following reports of chorioretinal atrophy in the post-marketing setting, a retrospective review of fundus photographs available from 38 out of the 41 patients enrolled in the Spark-sponsored interventional clinical studies was performed. In the phase 3 study, chorioretinal atrophy of the macula of treated eyes was found in 15.4% prior to treatment, in 42.6% at Year 1 and in 55.6% after Year 1. In the phase 1 study, chorioretinal atrophy of the macula was present in 35% prior to treatment, in 66.7% at Year 1 and in 73.9% after Year 1. Untreated control eyes showed the following rates of chorioretinal atrophy: 5.9% at baseline and 11.1% at Year 1 in the phase 3 study; 40% at baseline, 42.9% at Year 1 and 41.6% after Year 1 in the phase 1 study. Some of these atrophies involved the fovea. In the phase 3 study, there was involvement of the fovea in 1.9% of treated eyes prior to treatment, as well as at Year 1, and in 5.6% after Year 1. In the phase 1 study, the fovea was involved in 30% of treated eyes prior to treatment, in 38.9% at Year 1 and in 47.8% after Year 1. In the phase 3 study, atrophies in untreated control eyes did not involve the fovea. In the phase 1 study, 40% of atrophies in untreated eyes involved the fovea at baseline, 42.9% at Year 1 and 33.3% after Year 1.
Risk factors and risk groups	No risk factors or risk groups have been confirmed.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.8 • PL section 4 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-3 Important identified risk: increased intraocular pressure

Evidence for linking the risk to the medicine	These events have been seen in the clinical trials; Eight of the 41 (20%) subjects in the clinical program reported an event of intraocular pressure (IOP) increased. Overall, 10 (12%) of the 81 injected eyes had an event of intraocular pressure increased. One event was in an uninjected eye. Most were considered related to the administration of the product. In the literature increased IOP is a documented risk with the surgical procedure. Studies on eye surgery (vitrectomy) showed the incidence of increased IOP after surgery to range from 20-60%. In a prospective study in this type of eye surgery (pars plana vitrectomy), approximately 60% of patients had an acute IOP rise within 48 hours after surgery with no significant difference between IOP before and much later after the operation. In a study looking at data retrospectively on 111 eyes, after an average follow up of 49 months, there was no long term increase in IOP following eye surgery (pars plana vitrectomy). During the post-marketing phase, reports of IOP increase > 30 mmHg requiring treatment with IOP-lowering medication have been reported.
Risk factors and risk groups	Presence or history of glaucoma or elevated intraocular pressure. Complications from administration procedure. Raised IOP has also been associated with prolonged topical as well as systemic steroid use.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 and 4.8 • PL section 2 and 4 Recommendation for patients to avoid air travel or other travel to high elevations until the air bubble formed as a result of Luxturna administration has dissipated from the eye, which should be verified by an ophthalmic examination in SmPC section 4.4 and PL section 2 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-4 Important identified risk: retinal tear

Evidence for linking the risk to the medicine	Iatrogenic tears have been documented as a significant complication of vitrectomy with an incidence of about 5% (McCabe 2006). Another study reported a similar incidence of 6% in 219 eyes undergoing 20-gauge vitrectomy (Scartozzi et al 2007). However, other groups have reported a higher incidence of iatrogenic retinal tears; in a study of 645 eyes undergoing 20gauge vitrectomy, iatrogenic retinal breaks occurred in 15% of eyes intraoperatively, and resulting postoperative retinal detachment occurred in 2% of eyes (Ramkissoon et al 2010). Another study reported postoperative

	retinal detachment in 4% of 173 eyes undergoing 20-gauge vitrectomy for epiretinal membrane (Grewing and Mester 1996). Four of 81 (5%) eyes in 4/41 (10%) subjects administered voretigene neparvovec in the clinical studies had a retinal tear. The cumulative reporting rate for the risk during the post-marketing phase was 16 events (1.3%) per 1,171 treated eyes .
Risk factors and risk groups	Risk factors include myopia, lattice degeneration, previous eye surgery, and trauma. Complications from administration procedure.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 and 4.8 • PL section 2 and 4 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-5 Important identified risk: macular disorders

Evidence for linking the risk to the medicine	These events have been seen in clinical trials. Overall, 10 (12%) of 81 eyes administered Luxturna in 7 (17%) of 41 subjects in the clinical program reported events grouped as macular disorders (mapped to PT Eye disorder [foveal dehiscence], Macular hole, Macular degeneration [macular thinning], Maculopathy, and Retinal disorder [foveal thinning and loss of foveal function]). All events were considered related to the procedure and none were considered related to the product. From the literature a study of 45 patients undergoing eye surgery (pars plana vitrectomy) for fibrous covering of the macula due to unknown cause (idiopathic retinal membrane) one patient developed macular hole 6 months post-operatively. Wrinkling on the surface of the retina after vitrectomy for retinal detachment has been reported in 9-13% of eyes. Studies with subretinal administration of a similar viral vector, one group reported a measured thinning of the central macula after delivery of the vector, including 6 of 12 subjects with sustained reduction in macular thickness, through the last assessment at 24 or 36 months. Another group reported two out of 15 subjects with notable examples of foveal thinning in the short-term. Long-term follow-up in one of these two subjects showed that foveal thinning was still present at 24 months post subretinal administration. A third group reported minimal thinning observed within the first few months following treatment and remained stable throughout follow-up at 1 or more than 2 years. During the Spark-sponsored clinical program, one noteworthy case has been reported cumulatively. In this case, the patient had macular thinning with resultant permanent loss of foveal function (at one year follow-up visual acuity was 20/320 and full-field stimulus threshold was one decibel) in right eye.

Risk factors and risk groups	Risks include underlying retinal disorder, aging and vitreomacular traction. Complications from administration procedure.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 and 4.8 Advice in SmPC section 4.4 on where Luxturna should not be administered • PL section 2 and 4 Patients advised regarding which symptoms they should contact the doctor for in PL section 2 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-6 Important identified risk: cataract

Evidence for linking the risk to the medicine	These events have been seen in clinical trials. Cataract was reported in 21 (26%) of 81 eyes in 13 (32%) of 41 subjects in the clinical program. Of these, 18 events in 18 eyes were assessed as related to the subretinal administration procedure. Patients with hereditary retinal degeneration have a higher incidence of cataract formation and at a younger age. In a study describing the natural history of retinal degenerative disease in individuals with autosomal recessive mutations in the RPE65 gene, cataracts or other cloudiness of the lens were seen in at least one eye in 14 (20.0%) subjects: 11 (78.5%) had bilateral lens abnormalities, 2 subjects had lens abnormalities in only the right eye and one subject had a lens abnormality in only the left eye. The average age of subjects at the time of first lens abnormality was 26 years of age. After vitrectomy surgery, after 6 months, progression of clouding of the lens (nuclear sclerotic cataract progression) was seen in 60/74 (81%) of eyes compared to 13/74 (18%) with no surgery, and 100% of eyes had progression of cataract after 2 years compared to 8% of eyes with no surgery. In a retrospective review of eyes post vitrectomy surgery for macular fibrosis, 80/100 eyes developed cataract leading to significant problems with vision or had undergone cataract extraction compared to 24/100 in the group without surgery. During the post-marketing phase none of the cases associated with cataract led to severe or permanent visual impairment.
Risk factors and risk groups	Risks include aging, trauma, and vitrectomy. Also associated with inherited retinal disease.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.8 • PL section 2 and 4

	Patient advised regarding which symptoms they should contact the doctor for in PL Section 2 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-7 Important identified risk: intraocular inflammation and/or infection related to the procedure

Evidence for linking the risk to the medicine	These events have been seen in the clinical trials. Events grouped as eye inflammation and/or infection (mapped to PT Eye inflammation) was reported in 5 of 81 (6%) eyes in 3 of 41 (7%) subjects in the clinical program, including one event in one eye (1/81, 1%) of intraocular infection (culture-positive endophthalmitis). All events were considered related to the procedure. In the literature, it is noted that infection inside the eye (endophthalmitis) can occur after eye surgery (vitrectomy) for any cause, but it is rare. The incidence of endophthalmitis post pars plana vitrectomy has been reported to be between 0.03% and 0.07%. The rate of infection inside the eye after surgery for lens implantation was 0.2%. During the post-marketing phase, serious cases of intraocular inflammation associated with visual impairment have been reported cumulatively.
Risk factors and risk groups	Risks include incorrect administration procedure technique.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2, 4.3, 4.4 and 4.8 • PL section 2 and 4 Guidance regarding aseptic technique and use of topical microbicide in SmPC section 4.2. States what symptoms the patients need to be informed to report without delay in SmPC section 4.4 and PL section 2. Avoidance of swimming in SmPC section 4.4 and PL section 2. • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)

	See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-8 Important identified risk: retinal detachment

Evidence for linking the risk to the medicine	Retinal tear and detachment are well- known complications of vitrectomy surgery. Rhegmatogenous retinal detachment is the most common type of retinal detachment and develops when a tear in the retina causes fluid accumulation, resulting in the separation of retinal layers from the underlying RPE. Two (2.5%) of 81 eyes in two (5%) of 41 subjects administered voretigene neparvovec in the clinical program had a retinal detachment. Both events (one per subject) were assessed as related to the subretinal administration procedure. In the literature, in a study of 645 eyes undergoing vitrectomy, retinal tears occurred in 15.2% of eyes intraoperatively, and resulting postoperative retinal detachment occurred 1.7% of eyes at a median of 7.5 weeks (range 3-40 weeks). Another study reported postoperative retinal detachment in 4% of 173 eyes undergoing vitrectomy for fibrous membrane removal, with a mean time to presentation at 3.75 months after vitrectomy.
Risk factors and risk groups	These events are usually spontaneous and cannot be predicted. Myopia, lattice degeneration, pars plana vitrectomy, trauma, and family history are risk factors for retinal detachment.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2 and 4.4 • PL section 2 and 4 States what symptoms the patients need to be informed to report without delay in SmPC section 4.4 and PL section 2 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-9 Important potential risk: tumorigenicity

Evidence for linking the risk to the medicine	This is an advanced therapeutic medicinal product (ATMP)-specific risk consideration.
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401)

	• Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-10 Important potential risk: host immune response

Evidence for linking the risk to the medicine	Evidence from the literature. This is also an ATMP specific risk consideration.
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2 • PL section 3 The immunomodulatory regime to be used is stated in the SmPC section 4.2 and referenced PL section 3. • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-11 Important potential risk: third party transmission

Evidence for linking the risk to the medicine	ATMP specific risk consideration – Environmental Risk Assessment There were no instances of third party transmission noted during the clinical development. During the post-marketing phase, no cases of suspected or confirmed third party transmission have been reported.
Risk factors and risk groups	Healthcare workers, caregivers or other close contacts of the treated individual (partners and family members) including pregnant women and immunosuppressed individuals are particularly at risk of third party transmission.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4, 5.2 and 6.6 Advice on how to handle waste material from dressings, tears and nasal secretions and on personal protective equipment in section 4.4. An exclusion from donation of blood, organs, tissues, and cells for transplantation is included. Advice on managing accidental exposure is in section 6.6. • PL section 2 PL section 2 provides advice on personal protective equipment and disposal of dressings and waste materials. An exclusion from donation of blood, organs, tissues, and cells for transplantation is included. • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-12 Missing information: long-term efficacy (> 4 years)

Risk minimization measures	Routine risk minimization measures: • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-13 Missing information: use in pregnancy and lactation

Risk minimization measures	Routine risk minimization measures: • SmPC section 4.6 • PL section 2 • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-14 Missing information: use in children < 3 years of age

Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2 • PL section 2 • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-15 Missing information: long-term safety (> 9 years)

Risk minimization measures	Routine risk minimization measures: • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

Table 13-16 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study
A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401)	The objective of this registry-based study is to collect long-term safety information (i.e., for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)	This is a long-term safety and efficacy follow-up study of trial participants who received Luxturna in the clinical program.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Luxturna under this category.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Targeted Follow-up Checklist

Important identified risk: Vision loss due to progressive chorioretinal atrophy

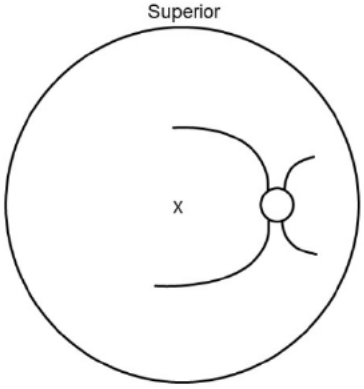
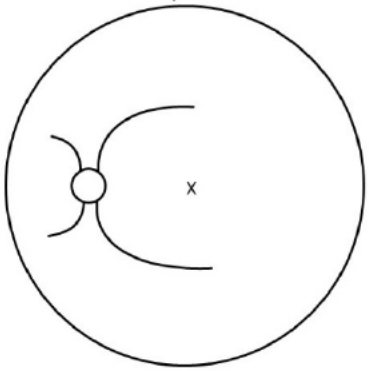
Luxturna (voretigene neparvovec) – (Retinal) atrophy at injection site and/or progression of atrophy

Adverse Event Description

Please provide and/or confirm the following additional information for the adverse event (AE)

(Reported Verbatim, [laterality]): _____ (Reported AE start date): _____

Please fill the below questions with respect to **Luxturna-treated** eye/s **observed with the adverse event**.

Information	**Right eye**	**Left eye**
Affected Eye *Please schematically depict* ***retinotomy sites and area(s) of reported AE of atrophy***	Superior  	Superior 
Location of the AE of atrophy	**(TICK ALL that apply)** ☐ Fovea (within 500 microns of foveola) ☐ Macula and within the arcades ☐ Retina outside posterior pole	**(TICK ALL that apply)** ☐ Fovea (within 500 microns of foveola) ☐ Macula and within the arcades ☐ Retina outside posterior pole
Location of the AE of atrophy relative to estimated area treated with Luxturna	**(TICK ALL that apply)** ☐ At the injection (retinotomy) site ☐ Inside the bleb area (other than retinotomy site) ☐ Outside the bleb area ☐ Other (*please specify)*: _____	**(TICK ALL that apply)** ☐ At the injection (retinotomy) site ☐ Inside the bleb area (other than retinotomy site) ☐ Outside the bleb area ☐ Other (*please specify)*: _____
Extent of the atrophic area(s) for the reported AE (estimated total)	_____ *(estimated number of disc areas)* ☐ Cannot be estimated from available data	_____ *(estimated number of disc areas)* ☐ Cannot be estimated from available data
Is this AE considered a progression of a previously	☐ Yes ☐ No (new event) ☐ Cannot be specified If yes, please provide: ☐ Expansion of the initial atrophy lesion	☐ Yes ☐ No (new event) ☐ Cannot be specified If yes, please provide: ☐ Expansion of the initial atrophy lesion

reported AE of atrophy?	☐ Atrophy at new location of the retina ☐ Unknown	☐ Atrophy at new location of the retina ☐ Unknown
Is this AE considered an expansion of depigmentation or atrophy present prior to treatment?	☐ Yes ☐ No ☐ Cannot be specified If yes, please specify: _____ _____	☐ Yes ☐ No ☐ Cannot be specified If yes, please specify: _____ _____
Last ophthalmic exam prior to the AE of atrophy (Date)	_____ / _____ / _____(*dd/mm/yyyy*)	_____ / _____ /_____(*dd/mm/yyyy*)
Kindly provide the suspected causality for the reported AE of atrophy	**(TICK ALL that apply)** ☐ Suspected to Luxturna drug ☐ Suspected to administration procedure	**(TICK ALL that apply)** ☐ Suspected to Luxturna drug ☐ Suspected to administration procedure
Kindly provide a rationale for above causality assessment	_____ _____	_____ _____
Did the AE of atrophy cause any impact on visual acuity (VA)?	☐ Yes ☐ No ☐ Cannot be determined ☐ Not assessed If yes, please provide: VA before event _____ (Unit) _____ (*dd/mmm/yyyy*): _____/_____/_____ VA post event _____ (Unit) _____ (*dd/mmm/yyyy*): _____/_____/_____	☐ Yes ☐ No ☐ Cannot be determined ☐ Not assessed If yes, please provide: VA before event _____ (Unit) _____ (*dd/mmm/yyyy*): _____/_____/_____ VA post event _____ (Unit) _____ (*dd/mmm/yyyy*): _____/_____/_____
Did the AE of atrophy cause any impact on FST?	☐ Yes ☐ No ☐ Cannot be determined ☐ Not assessed If yes, please provide: FST before event _____ (Unit) _____ (*dd/mmm/yyyy*): _____/_____/_____ FST post event _____ (Unit) _____ (*dd/mmm/yyyy*): _____/_____/_____	☐ Yes ☐ No ☐ Cannot be determined ☐ Not assessed If yes, please provide: FST before event _____ (Unit) _____ (*dd/mmm/yyyy*): _____/_____/_____ FST post event _____ (Unit) _____ (*dd/mmm/yyyy*): _____/_____/_____
Was there any defect in visual field observed associated with the adverse event?	☐ Yes ☐ No ☐ Cannot be determined ☐ Not assessed	☐ Yes ☐ No ☐ Cannot be determined ☐ Not assessed If yes, please specify: _____

	If yes, please specify: _____	
Which method was used to diagnose the AE of atrophy?	**(TICK ALL that apply)** ☐ Color fundus photography ☐ Pseudocolor image of retina ☐ Fundus autofluorescence imaging ☐ OCT If OCT was performed, please provide: Layers of the Retina involved: (Tick ALL that apply): ☐ Sensory retina (neuroretina) ☐ Retinal pigment epithelium ☐ Choroid ☐ Cannot be specified ☐ Any other investigative modality (please specify):_____	**(TICK ALL that apply)** ☐ Color fundus photography ☐ Pseudocolor image of retina ☐ Fundus autofluorescence imaging ☐ OCT If OCT was performed, please provide: Layers of the Retina involved: (Tick ALL that apply): ☐ Sensory retina (neuroretina) ☐ Retinal pigment epithelium ☐ Choroid ☐ Cannot be specified ☐ Any other investigative modality (please specify):_____

Patient History and treatment information

Patient received Luxturna treatment in which eye: ☐ Right eye ☐ Left eye

What is the underlying disease indication:

☐ Lebers congenital amaurosis type 2 ☐ Early onset retinal dystrophy (EORD) ☐ Early onset severe retinal dystrophy (EOSRD) ☐ Severe early childhood onset retinal dystrophy (SECORD) ☐ Retinitis pigmentosa ☐ Others

Were there any intraoperative complications which could have possibly contributed to the adverse event of retinal atrophy:

☐ Yes ☐ No

If yes, please specify the complication with action taken (specify each eye):

_____

Was more than one injection bleb created?

Right eye: ☐ Yes ☐ No. If yes, specify number of blebs _____ and total volume (for all blebs) administered _____ [mL]

Left eye: ☐ Yes ☐ No. If yes, specify number of blebs _____ and total volume (for all blebs) administered _____ [mL]

Any relevant medical history:

Right eye: -Presence of myopia: ☐ Yes ☐ No . If Yes, please specify the Diopter _____

-Any other_____

Left eye: -Presence of myopia: ☐ Yes ☐ No. If Yes, please specify the Diopter_____

-Any other_____

Was an injection technique or materials different from the ones described in surgical manual used?

☐ Yes ☐ No

If yes, (Tick ALL that apply)

Right eye:

☐ Use of automated injection system

☐ Creation of a saline Pre-bleb

☐ Different cannula/injection tubing

☐ Any other (please specify): _____

Left eye:

☐ Use of automated injection system

☐ Creation of a saline Pre-bleb

☐ Different cannula/injection tubing

☐ Any other (please specify): _____

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Approved key messages of the additional risk minimization measures

Physician educational material:

- **The Summary of Product Characteristics**
- **Surgical education for the administration of Luxturna:**
  - Information on the administration of Luxturna
  - Description of materials and procedures needed to perform subretinal injection of Luxturna
- **Pharmacy training manual for preparation of Luxturna:**
  - Information on preparation of storage of Luxturna
- **The patient information pack:** Patient information leaflet
  - Package leaflet will be available in alternate formats including large print and as an audio file. Information on how to obtain the special formats will be provided in the package leaflet.
- **Patient card**
  - Highlights the importance of follow-up visits and reporting side effects to the patient's physician.
  - Inform healthcare professionals that the patient has received gene therapy, and the importance of reporting adverse events.
  - Contact information for adverse event reporting.
  - Patient card will be available in alternate format including large print and as an audio file. Information on how to obtain the special formats will be provided in the patient card.