Taiwan Food and Drug Administration

Assessment Report

Trade Name：
樂適達注射劑/ Luxturna concentrate and solvent for solution for injection
"諾華"樂喜達注射劑/ "Novartis" Luxturna concentrate and solvent for solution for injection

Active Ingredient：Voretigene neparvovec

License Number：MOHW-OBI 000044/MOHW-BI 001209

Applicant：台灣諾華股份有限公司

Approval Date：111.12.21

Indication：
適用於因雙對偶基因 *RPE65* 突變之遺傳性視網膜失養症(inherited retinal dystrophy，IRD)，而喪失視力，並具有足夠的存活視網膜細胞的病人。

Treatment of patients with vision loss due to inherited retinal dystrophy (IRD) caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells.

Background Information

Trade Name	樂適達注射劑/ Luxturna concentrate and solvent for solution for injection "諾華"樂喜達注射劑/ "Novartis" Luxturna concentrate and solvent for solution for injection
Active Ingredient(s)	Voretigene neparvovec
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	注射液劑/ $5X10^{12}$vg/ml
Indication	適用於因雙對偶基因 *RPE65* 突變之遺傳性視網膜失養症(inherited retinal dystrophy，IRD)，而喪失視力，並具有足夠的存活視網膜細胞的病人。 Treatment of patients with vision loss due to inherited retinal dystrophy (IRD) caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells.
Posology	詳見仿單
Pharmacological Category **ATC Code**	S01XA27

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

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

The starting materials for manufacture of voretigene neparvovec active substance consist of a mammalian cell substrate and three purified recombinant DNA plasmids. A description of the derivation, characterization and manufacture of these plasmids has been provided. Detailed description of the origin, history and preparations of cell banks are provided. Adventitious and endogenous agent safety testing and identity for cell banks were conducted based on the recommendations in ICH Q5D. Raw materials of direct and indirect biological origin are also justified.

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

The voretigene neparvovec active substance has been sufficiently characterized by

physicochemical and biological state-of-the art methods revealing that the active substance has the expected structure.

Manufacturing process with in-process controls, process development histories, comparability studies, process validation, specification, analytical methods and validation, batch analyses, and reference materials are provided to demonstrate the quality and consistency of voretigene neparvovec.

Long-term, accelerated, and stress stability studies have been carried out for voretigene neparvovec (DS) batches and support the proposed shelf-life of DS.

2.1.2 Drug product

The commercial Drug Product (Luxturna) is supplied at a volume of 0.5 ml frozen sterile concentrate solution in a 2 mL single-dose vial with 5 x 10^{12} vector genomes per mL. The Luxturna is a frozen aqueous solution concentrate that requires a 1:10 dilution with diluent (solvent) prior to administration.

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

The composition of DP is listed. The excipients for DP are complied with USP-NF, and Ph. Eur. compendia specifications. There are no novel excipients in the DP. No excipients of human or animal origin are used in the DP.

DP manufacturing process and formulation development are described appropriately. The compatibility data is submitted adequately.

The release specification and stability specification for Luxturna are provided including appearance, general characteristic properties, quantity, identity, purity, activity/potency and safety. The batch analyses are provided and show that the manufactures of Luxturna are controlled properly and consistently.

The current data of long-term stability studies supports the shelf-life of Luxturna for 24 months under the storage condition of ≦-65°C.

In conclusion, information on the drug substance and finished drug product are provided appropriately to support the quality of Luxturna.

2.2 Nonclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The in vitro pharmacology studies showed that transduction of normal or mutant Briard RPE

cells with increasing vector doses resulted in a dose-dependent increase in RPE65 mRNA and protein. These studies demonstrate that the vector can infect relevant affected cells and produce the missing protein, i.e., RPE65. Two mouse models of RPE65 deficiency and a single canine disease model were utilized to establish proof-of-concept for this vector to treat this patient population. Following subretinal injection to these animals' eyes, RPE65 protein was found localized to the RPE cells, but not other retinal cell types, in the injected eyes and was absent from uninjected or sham-injected eyes. Expression of the protein correlated with significant improvement in retinal and visual functions in mice, improved ERGs and visual behavior, and reduced nystagmus in Briard (affected) dogs. Stand-alone safety pharmacology studies have not been performed following ICH S6 (R1). However, in all general safety studies, animals were subject to daily in-life clinical observations, and no reports of CNS, renal, cardiac, or respiratory distress have been reported.

Single-dose (including biodistribution) and repeated-dose toxicology studies were conducted in normal-sighted dogs, RPE65 mutant dogs, and normal-sighted non-human primates (NHPs) with the proposed clinical product, AAV2-hRPE65v2. Dosing regimens for the single-dose studies consisted of either unilateral administration or bilateral, simultaneous administration (dose up to 1.5 $x10^{12}$ vg in dogs and 7.5 $x10^{11}$ vg in NHP). Assessments of biodistribution were incorporated into the single and bilateral, simultaneous dose toxicology and biodistribution studies in dogs and NHPs. Intraocular fluids (anterior chamber fluid and vitreous) of all test article-treated eyes were strongly positive for vector sequence. Optic nerves (and optic chiasms) of the test article-treated eyes were often weakly positive for vector sequence; this was likely a consequence of exposure to retinal ganglion cells. Low levels of test article were observed in the spleen and, to a lesser extent, the liver. Notably, there was no vector dissemination to the gonads. The data demonstrated that the subretinal administration of AAV2-hRPE65 results in minimal vector dissemination outside of the ocular space.

2.2.2 Toxicological Studies

Several subretinal dosing regimens were employed for the repeated-dose studies. Safety studies performed in dogs and NHPs evaluated both local and systemic toxicity. Occasional inflammation in the retina, attributed to the surgical delivery procedure, was detected, and no definitive vector-related adverse effects were observed in non-ocular tissues. Subretinal injection of 1.5x 10^{12} vg/eye of a precursor AAV2-hRPE65v2 vector product in normal-sighted dogs resulted in ocular inflammation and retinal degeneration histologically in regions exposed to the vector. This dose level is 10-fold higher than the clinical dose level of 1.5 x 10^{11} vg/eye. The NOAEL in NHPs was 7.5 x 10^{11} vg/eye, 5-fold higher than the proposed clinical dose. The histopathological findings in the eye suggested that there may be a mild immune response due to the re-administration of AAV2-hRPE65v2 sequentially to the same eye in the RPE65 mutant dogs. However, the re-administration of AAV2-hRPE65v2 to the same eye is not specified in

the applicant's labeling. There was no evidence of a pro-inflammatory T cell response to the AAV2 capsid or RPE65 protein in the NHPs, except for one NHP previously exposed to AAV2 vector that developed a CD4+ T cell response. A limited T cell response to human RPE65 was observed in RPE65 mutant dogs.

Antibodies to human RPE65 were detected transiently in isolated cases in dogs and NHPs. Antibodies to the AAV2 capsid were detected in the anterior chamber fluid and/or serum of normal and RPE65 mutant dogs and in NHPs previously exposed to AAV2 vector. Genotoxicity, carcinogenicity, and reproductive toxicology studies were not conducted. The applicant provided the appropriate and acceptable justification based on the biological attributes of AAV2-hRPE65v2, the current scientific publications, and the pharmacology and toxicology data.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Sponsor provided one Phase III study (AAV2-hRPE65v2-301) to support the efficacy of Luxturna concentrate and solvent for solution for injection (Voretigene neparvovec 5 x 10^{12} vg/ml) for the claimed indication. The major design features and results of this study were summarized as follows:

- **Study AAV2-hRPE65v2-301:**

The study was a Phase 3, open-label, randomized controlled trial of gene therapy intervention by subretinal administration of AAV2-hRPE65v2 1.5 x 10^{11} vg (0.3 ml) for each eye. The dosing interval between eyes ranged from 6 to 18 days.

Subjects were randomized in a 2:1 ratio to the Intervention or Control group, stratified by Screening age (≥ 10 years or < 10 years) and mobility testing category (≥ 125 lux or < 125 lux). Within each stratum, randomized blocks (block size of 3) governed the allocation to treatment group.

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

To maintain strict control of Type I error rate, the three secondary outcomes were to be tested hierarchically:

- If the primary outcome was statistically significant, full-field light sensitivity threshold (FST) was to be tested at a two-sided Type I error rate of 0.05.
- If FST was statistically significant, the monocular mobility change score was to be tested

at a two-sided Type I error rate of 0.05.

- If the monocular test was statistically significant, visual acuity was to be tested at a two-sided Type I error rate of 0.05.

For the ITT population, the mean multi-luminance mobility test (MLMT) change score was 1.8 for the Intervention group and 0.2 for the Control group, resulting in a mean difference (95% CI) of 1.6 (0.72, 2.41). This MLMT change score difference was statistically significant (p=0.001) from both the observed and permutation test p-values. Similar results were observed for the mITT (1.6 [0.76, 2.50]; p=0.004) and PP (1.7 [0.79, 2.56]; p=0.004) analysis populations.

For the ITT population, analysis of the FST results averaged over both eyes showed a mean change from Baseline to Year 1 of -2.08 log10 (cd.s/m^2) for the Intervention group and 0.04 log10 (cd.s/m^2) for the Control group, for a statistically significant ($p < 0.001$) between-group mean (95% CI) treatment difference of -2.11 (-3.19, -1.04) log10 (cd.s/m^2).

For the monocular MLMT change score for the first-treated eye, the mean change from Baseline to Year 1 was 1.9 for the Intervention group and 0.2 for the Control group, resulting in a statistically significant (p=0.001) mean (95% CI) treatment difference of 1.7 (0.89, 2.52).

Analysis of visual acuity averaged over both eyes showed a mean change from Baseline to Year 1 of -0.16 LogMAR for the Intervention group and 0.01 LogMAR for the Control group, resulting in a non-significant (p=0.17) mean (95% CI) treatment difference of -0.16 (-0.41, 0.08).

2.4.2 Safety Results

Phase 1 studies 101, 102 (follow-on study of 101), and Phase 3 study 301 contributed the safety database of AAV2-hRPE65v2. A total of 41 subjects and 81 eyes had exposed to AAV2-hRPE65v2 in clinical studies.

The main safety concerns of Luxturna administration include increased intraocular pressure, intraocular infection and/or inflammation, cataract, retinal abnormalities (e.g., retinal tears, retinal detachment, macular holes, foveal thinning, foveal dehiscence), which may occur following vitrectomy and/or subretinal injection. These risks may be mitigated through controlled distribution, education program and closely monitor relevant symptoms and signs.

Chorioretinal atrophy has been identified from post-marketing experience. Pharmacovigilance with targeted follow-up checklist is required.

2.5 Bridging Study Evaluation

The vector shedding into tears and peripheral blood appeared to be transient and low. The elimination is unlikely to be influenced by the genetically determined metabolic polymorphisms. The are no major differences in pathophysiologic process, disease diagnosis and management between Taiwanese and non-Taiwanese patients. Although different types of mutation in *RPE65* gene has been identified in Chinese population, Luxturna is designed to restore the RPE65 protein function regardless of the type of mutation. Overall, the ethnic differences of efficacy and safety are expected to be minimal.

2.6 Conclusion

In conclusion, Luxturna as a treatment for patients with inherited retinal dystrophy (IRD) caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells demonstrates a favorable risk-benefit profile to recommend regular approval.

3. Post-Marketing Requirements

(1) Interim and final study reports of long-term follow-up Study LTFU-01 should be submitted once available.
(2) Final study report of Japanese Study CLTW888A11301 should be submitted once available.
(3) Luxturna-treated patients in Taiwan should be enrolled in the global post-authorization safety Study CLTW888A12401.