Cost-effectiveness of voretigene neparvovec (Luxturna®) for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of voretigene neparvovec (Luxturna®). Following assessment of the Applicant's submission, the NCPE recommends that voretigene neparvovec (Luxturna®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The HSE asked the NCPE to carry out an assessment of the Applicant's (Novartis Pharmaceuticals) economic dossier on the cost effectiveness of voretigene neparvovec (Luxturna®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **September 2020**

Summary

In April 2020, Novartis Pharmaceuticals submitted a dossier of evidence on cost effectiveness to support the reimbursement application for voretigene neparvovec (Luxturna®) 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. Novartis Pharmaceuticals are seeking reimbursement in the hospital setting. Voretigene neparvovec is classified as an advanced therapeutic medicinal product (ATMP).

Voretigene neparvovec is a gene transfer vector that employs an adeno-associated viral vector serotype 2 (AAV2) capsid as a delivery vehicle for the human *RPE65* protein complementary deoxyribonucleic acid (cDNA) to the retina. It is manufactured as a single-dose vial containing concentrate and solvent for solution for injection. Administration of voretigene neparvovec into the subretinal space results in transduction of retinal pigment epithelial cells with a cDNA encoding normal human *RPE65* protein (gene augmentation therapy), providing the potential to restore the visual cycle.

Voretigene neparvovec is administered as two subretinal injections, one to each eye, (no fewer than six days apart) once per lifetime. Prior to administration (approximately three days before), patients are required to receive an immunomodulatory regimen (such as prednisolone), which is expected to be continued for a further 18 to 30 days, depending on the timing of the administration to the other eye.

The main comparator for this analysis is best supportive care (BSC) which involves provision of supportive measures. This includes assignment to an eye clinic liaison officer, procuring mobility aids, and provision of psychological support where required.

1. Comparative effectiveness of voretigene neparvovec

The Applicant included evidence from two trials. The pivotal trial for the submission was Study 301/302; an open-label, multi-centre, phase III randomised controlled trial. A total of 31 patients were recruited (intention to treat [ITT] population; n=21 voretigene neparvovec

and n=10 control). One patient from each arm withdrew following randomisation but prior to receipt of assigned treatment (modified intention to treat [mITT] population; n=20 voretigene neparvovec and n=9 control). The Applicant states that the comparator for Study 301 is BSC, but it is not specifically described. The control arm became eligible to receive treatment with voretigene neparvovec one year after baseline. Study 301 refers to the first year of the study where voretigene neparvovec was compared to control. Study 302 refers to the continuation phase where the control arm had also received treatment with voretigene neparvovec; for Study 302 the intervention and control arms are thereafter referred to as the original intervention arm and the delayed intervention arm. Study 302 is ongoing and data up to four years follow-up was presented in the submission. Study 101/102 is an open-label, phase I, single-arm trial. Study 101 employed a dose ranging design; with patients (n=12) receiving either a 'low', 'medium', or 'high' dose of voretigene neparvovec in a single (worse, non-preferred) eye. After one year, Study 101 ended and patients (n=11) could enter Study 102, a long term follow up for up to 15 years. In this study, patients had one injection of voretigene neparvovec in the eye not treated in Study 101. Data at 7.5 years follow up are available from the follow up study. Study 101/102 was not designed or powered to assess the clinical efficacy of voretigene neparvovec. Therefore the emphasis on clinical efficacy is given here to Study 301/302.

The primary outcome measure for study 301/302 was the mean change in multiluminance mobility test (MLMT) score. The MLMT score was devised by the Applicant and measures the effect of functional vision in a quantitative and standardised way at specified light levels. It is not used in clinical practice. Other more widely used measures such as visual acuity (clarity of vision) and full field light sensitivity were evaluated as secondary endpoints, with visual field (range of vision) evaluated as an exploratory endpoint.

Results from study 301/302 showed that, at year one, patients in the voretigene neparvovec arm had improved MLMT scores compared with no improvement in the control arm. The difference was statistically significant (mean difference 1.60; 95% confidence interval [CI] 0.72 to 2.40; p=0.0013). The Applicant proposed an MLMT score change of 1 or more as clinically meaningful. However, the Review Group note that this is subject to some uncertainty. Improvements in the MLMT score seemed to remain steady until three-year

follow up. At year three, the proportion who passed the MLMT at one lux (lowest light level) was 60% (12 out of 20) in the original intervention arm and 89% (8 out of 9) in the delayed intervention arm (Study 302). This indicated a sustained improvement in functional vision for patients who had voretigene neparvovec.

Visual acuity was measured using the Early Treatment of Diabetic Retinopathy (ETDRS) scale, with the scale adapted from Holladay to assign values for off-chart acuities. There was no statistically significant difference in changes in visual acuity from baseline to year one between voretigene neparvovec and control (-0.16 LogMAR, 95% CI −0.41 to 0.08; p=0.17, which corresponded to a gain of 8.1 letters on the eye chart). A post-hoc analysis using the ETDRS scale adapted from Lange and colleagues found comparable results, although differences reached statistical significance (9.0 letters in the intervention group vs. 1.6 letters in the control group; difference of 7.4 letters; 95% CI 0.1 to 14.6; post-hoc p=0.0469). A change of visual acuity of 0.3 LogMAR is considered clinically meaningful (or a gain of 15 letters on the ETDRS eye chart). At one-year post-voretigene neparvovec treatment, clinically meaningful improvements in visual acuity were observed in 14 participants in the voretigene neparvovec arm (n=20) (Study 301). Following cross-over to voretigene neparvovec, improvements in visual acuity of 0.3 logMAR were observed in three delayed intervention arm participants one year following administration of treatment (Study 302). At year three, mean (SD) change in visual acuity from baseline was -0.16 (0.35) logMAR (gain of eight letters) in the original intervention arm (three years post-voretigene neparvovec treatment) and -0.06 (0.23) (gain of three letters) in the delayed intervention arm (two years post voretigene neparvovec treatment) (Study 302).

Full-field light sensitivity testing (FST) was also performed. Light sensitivity testing is performed to assess photoreceptor response and a subject's perception of light sensitivity at different luminance levels. For this measure, a negative result indicates improved light sensitivity. Participants in the voretigene neparvovec arm saw an improvement in white light FST between baseline and year one with no improvement at year one in the control group (difference between groups: -2.11, 95% CI, -3.19 to -1.04) (Study 301). While the results of the FST testing corroborate and support the results of the MLMT, the direct clinical benefit of FST is not clear. The improvements were sustained for four years (three years in the delayed intervention arm) (n=21 participants assessed) (Study 302).

Visual field improved for participants who received voretigene neparvovec compared with participants who received control. Goldmann Visual Field measurement showed a statistically significant difference in total sum degrees in the voretigene neparvovec arm compared with the control arm at year one (mean difference 378.7, 95% CI 145.5 to 612.0; p=0.0059) (Study 301). The improvement in visual field seen by year one was sustained for three years (Study 302).

The Applicant also used data from the "Natural History of Individuals with Retinal Degeneration Due to Autosomal Recessive Mutations in the *RPE65* Gene (*RPE65* NHx)" study. *RPE65* NHx was a retrospective chart review of 70 patients with *RPE65*-mediated inherited retinal dystrophies (IRD) who would be eligible to receive voretigene neparvovec. Patients had a mean age of 15 years at the start of data collection, and were followed up for a mean duration of 7.28 years. The study collected clinical data from seven global, tertiary referral centres for retinal degenerative diseases. Information collected and analysed included demographic data, and measurements of visual acuity and and visual field. There were a total of 309 and 331 measurements of visual acuity for the left and right eyes, respectively, collected from 68 patients. The general pattern observed was that of marked impairment but fairly stable visual acuity during the first decade of life, with gradual worsening beginning to occur around the ages of 15 to 20 years, and subsequent rapid acceleration of the rate of visual acuity loss after the age of 20 years. Visual field assessments were collected primarily using manual Goldmann kinetic perimetry, measured as sum total degrees. A total of 161 measurements for the left eye and 160 measurements for the right eye were collected from 27 subjects. Each subject had a varying number of measurements. On average, in this cohort, a one-year increase in age decreased the Goldmann test stimulus type III4e visual field by approximately 25 sum total degrees in each eye; the V4e visual field decreased by approximately 37 sum total degrees in each eye.

The Review Group's main concerns relating to the clinical effectiveness evidence in the pivotal trial include (i) interpretation of the measured outcomes and (ii) duration of treatment effect of voretigene neparvovec. First, the primary endpoint used in the phase III clinical trials, the MLMT, was designed to capture a critical aspect of the disease process (i.e. being unable to navigate in low light); however, the test itself has not been correlated to

outcomes measured in a real-world setting. As such, there remains uncertainty regarding what a one to two-unit improvement in MLMT score means for individuals as they go about their day-to-day activities. Secondly, long-term efficacy remains a question for this treatment. Individuals with bialleleic *RPE65* mutations have significant retinal degeneration leading to worse functional vision over time. The evidence with regard to the permanent therapeutic effects of gene therapy has not been established. It should also be noted that the number of patients recruited to the clinical development programme for voretigene neparvovec was small (12 subjects in phase I and 31 subjects in phase III studies). While this could be considered representative of the rare nature of *RPE65*-mediated IRD, small patient numbers are associated with greater uncertainty regarding generalisability of treatment effect to the general population.

2. Safety of voretigene neparvovec

A total of 41 patients, aged 4 to 45 years, received treatment with voretigene neparvovec over the course of phase I and phase III studies. All subjects experienced at least one adverse drug reaction (ADR). Most were mild and resolved without sequalae. In phase I studies (n=12), the most frequently reported ADRs were conjunctival hyperaemia (67%), pyrexia (58%) and leuckocytosis (50%). In phase III studies, the most frequently reported ADRs for subjects in the original intervention arm of Study 301 (n=29) during the first year post injection were headache (45%), leukocytosis (38%), nausea (35%) and vomiting (35%). Three cases of retinal deposits considered to be related to voretigene neparvovec were reported as non-serious ADRs in three of 41 (7%) subjects. All three cases were transient and resolved without sequalae by eight weeks. Serious ADRs related to the administration procedure were reported in three subjects during the clinical programme. These included: one case of increased intraocular pressure associated with treatment for endophthalmitis resulting from the administration procedure; one case of loss of foveal function; and one case of retinal detachment. The most common ADRs (incidence ≥5%) related to the administration procedure were conjunctival hyperaemia, cataract, increased intraocular pressure, retinal tear, dellen, macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain and maculopathy. To minimise risk associated with the administration procedure, a condition of the marketing authorisation is that voretigene neparvovec will

only be distributed through specialist centres where the relevant personnel have completed mandatory training on use of the product.

3. Cost effectiveness of voretigene neparvovec

The cost-effectiveness of voretigene neparvovec was evaluated using a de novo Markov model and compared to BSC. The states in the model comprised five alive health states based on differing levels of vision impairment, and a sixth "absorbing" death state. Patient transitions from baseline to year one were informed by the pivotal trial, Study 301, whereas long-term transitions were informed by a combination of clinical expert opinion regarding the long-term effect of voretigene neparvovec and a multistate model fitted to natural history data from the *RPE65* NHx study. Mortality multipliers, which increased rates of general mortality in the modelled patient population from the general population, were drawn from a study by Christ et al (2014). Outcomes within the model were based on a combination of visual acuity (Holladay scale) and visual field (Goldmann perimetry testing) measurements.

Health state utility values were derived from a bespoke vignette study (Acaster-Lloyd) involving interviews with six UK-based clinicians conducted by the Applicant. Costs were derived from published sources. The included cost categories considered treatment acquisition, administration, surgery, monitoring, medical resource use, resolution of adverse events, and eligibility testing. Medical resource use utilisation was informed through a combination of assumptions made by the Applicant and input from clinical experts.

The Review Group had concerns with the approaches and assumptions used by the Applicant in their economic model, primarily relating to claims about the duration of treatment effect of voretigene neparvovec. Other areas of concern included: the elicitation exercise used to inform health state utilities, the use of limited datasets to inform baseline health state distributions and to calculate transition probabilities, as well as the assumptions used for patient transitions when no data were available from the pivotal trial. The key driver of the model was the duration of treatment effect in patients treated with voretigene neparvovec.

Results

The Review Group explored the uncertainty by applying adjustments to the Applicant's model to derive their adjusted base case, choosing to pool data from the *RPE65* NHx study with Study 301/302 to derive an alternative baseline health state distribution; to use a health state utility set derived from Rentz et al (2014) as it may have been subject to less bias than the vignette study conducted by the Applicant; including crossover data to calculate transition probabilities; assuming patients who had no data available from Study 301/302 remained in the same health state; and did not apply a mortality multiplier or a residual treatment effect. The NCPE adjusted ICERs (Table 1) and the Applicant base case ICERs (Table 2) are shown.

Table 1: NCPE Review Group adjusted base case analysis*

Treatment	**Incremental Costs (€)**	**Incremental QALYs**	**ICER (€ per QALY)**
BSC			
VN	€688,606	3.64	€189,037/QALY

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio; **BSC** Best Supportive Care
VN voretigene neparvovec
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2: Applicant base case analysis*

Treatment	**Incremental Costs (€)**	**Incremental QALYs**	**ICER (€ per QALY)**
BSC			
VN	€687,508	4.63	€148,473/QALY

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio; **BSC** Best Supportive Care
VN voretigene neparvovec
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

A probabilistic analysis of the NCPE adjusted base case, resulted in an ICER of €181,031/QALY (95% CI €101,402 to €2,411,271). The probability of cost effectiveness at both €45,000/QALY and €20,000/QALY using the NCPE adjusted base case was 0%.

4. Budget impact of voretigene neparvovec

The price to wholesaler for voretigene neparvovec is €690,000 (for two single-use packs), administered as two subretinal injections (one in each eye) on separate occasions no fewer

than six days apart. The cost per patient per once-off treatment course with voretigene neparvovec, including VAT, is €810,750.

Based on estimates of incidence from the literature and assumptions regarding prevalence, the Applicant assumes that eight prevalent and one incident patient will be treated within the first five years of voretigene neparvovec becoming available. It is assumed that these patients will be treated at a rate of two per year for the first four years to account for product availability and healthcare system resourcing. The Review Group considers there to be uncertainty associated with the Applicant's estimated eligible patient population, in particular the method used to estimate incidence rate. The Review Group also has concerns regarding the assumption that 55% of patients will have viable retinal cells making them eligible for treatment. Considering that a characteristic feature of *RPE65*-mediated IRDs is the early age of manifestation of disease, and clinical opinion has indicated a preference to treat patients with voretigene neparvovec at an early age, the Review Group considers it probable that a much larger proportion of patients will have sufficient viable retinal cells.

Based on the Applicant's estimated patient numbers (n=9) and treatment timelines, the estimated cumulative gross budget impact of voretigene neparvovec over the next five years is €7.2 million. Since voretigene neparvovec is the first pharmacotherapeutic agent indicated for the management of vision loss associated with *RPE65*-mediated IRD, it is not anticipated to displace any other treatments. The Applicant considered additional costs associated with voretigene neparvovec treatment including administration costs, immunomodulatory regimen costs, monitoring costs and adverse event costs. The total net budget impact estimate for voretigene neparvovec, following incorporation of these additional costs, was calculated as €7.4 million (incl VAT).

The greatest area of uncertainty pertaining to the estimated budget impact analysis for voretigene neparvovec relates to the number of patients eligible for treatment with the drug. The Applicant conducted a scenario analysis where 95% of patients were assumed to have sufficient viable retinal cells making them eligible for treatment. The number of eligible prevalent patients increased from eight to 13; the number of incident patients increased from one to two. This resulted in a 5-year cumulative net budget impact of €12.3 million.

5. Patient Submission.

A patient submission was received during the course of this evaluation.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that voretigene neparvovec (Luxturna®) is not considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.*

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.