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CADTH DRUG REIMBURSEMENT REVIEW

# Pharmacoeconomic Report

## VORETIGENE NEPARVOVEC (LUXTURNA)

**(Novartis Pharmaceuticals Canada Inc.)**

**Indication:** Vision loss, inherited retinal dystrophy


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# Abbreviations

| | |
|---|---|
| **BIA** | budget impact analysis |
| **BSC** | best supportive care |
| **EQ-5D** | EuroQol 5-Dimensions |
| **ICER** | incremental cost-effectiveness ratio |
| **IRD** | inherited retinal dystrophy |
| **LCA** | Leber congenital amaurosis |
| **MLMT** | multi-luminance mobility test |
| **MSM** | multistate model |
| **OCT** | optical coherence tomography |
| **QALY** | quality-adjusted life-year |
| **RP** | retinitis pigmentosa |
| **RPE65** | retinal pigment epithelium 65 kDa protein |

# Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2 and a conclusion.

## Table 1: Submitted for Review

| Item | Description |
|---|---|
| Drug product | Voretigene neparvovec (Luxturna) 5 × $10^{12}$ vector genomes/mL concentrate in a single-use vial for solution |
| Submitted price | Voretigene neparvovec, 1.5 × $10^{11}$ vector genomes subretinal injection: $515,750 (per eye) |
| Indication | For the treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells<br><br>Disease-causing biallelic *RPE65* mutations should be confirmed by an accredited laboratory using validated assay methods |
| Health Canada approval status | NOC |
| Health Canada review pathway | Standard review |
| NOC date | October 13, 2020 |
| Reimbursement request | As per indication |
| Sponsor | Novartis Pharmaceuticals Canada Inc. |
| Submission history | Previously reviewed: No |

NOC = Notice of Compliance; RPE65 = retinal pigment epithelium 65 kDa protein.

## Table 2: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | • Cost-utility analysis<br>• Markov model |
| **Target population** | Individuals with *RPE65*-mediated inherited retinal dystrophy who have sufficient viable retinal cells, in accordance with Study 301 |
| **Treatment** | Voretigene neparvovec |
| **Comparator** | BSC. BSC includes low-vision aids and supportive services related to medical vision care and genetic counselling |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, blindness-free years |
| **Time horizon** | Lifetime (85 years) |
| **Key data source** | Study 301: an open-label, randomized controlled trial with patients receiving BSC crossed over at year 1 to receive voretigene neparvovec |
| **Submitted results for base case** | ICER = $103,075 per QALY (incremental cost = $951,878; incremental QALYs = 9.2) |

| Component | Description |
|---|---|
| **Key limitations** | • There is limited evidence on the duration of treatment effect. The sponsor assumed 40 years of treatment effect, which clinical experts considered to be highly optimistic.<br>• Natural history was informed by a retrospective chart review that had a high proportion of missing observations (~80%). Missing data imputed based on a last observation carried forward approach that is inappropriate due to the progressive nature of the condition. Disease progression was described by fitting a parametric multistate model to the data. The model enforced progression by removing any contradictory observations that demonstrated improvements over time, thereby omitting potential chance and measurement errors.<br>• Study 301 informed the comparative treatment effect estimates. As noted in the CADTH Clinical Review Report, this study had a small sample size with imbalances in baseline characteristics, resulting in a high risk of bias and less robust estimates.<br>• The health utilities used in the model were elicited from a small number of clinicians consulted by the sponsor rather than from the general population or the patient population studied in the pivotal trials.<br>• Time dependency in the fitted multistate model was unlikely aligned with the time dependency in the long-term natural history of patients within the Markov decision model. |
| **CADTH reanalysis results** | • In the CADTH reanalysis, the duration of the treatment effect was set at 10 years, data from the crossover arm of Study 301 was used to inform short-term transition probabilities, and revised utility values were used that included the additional estimates from the clinical experts consulted by CADTH.<br>• The ICER for voretigene neparvovec is $200,477 per additional QALY compared with BSC ($1,019,882 incremental costs, 5.09 incremental QALYs). The probability of voretigene neparvovec being cost-effective at a willingness-to-pay threshold of $50,000 per QALY is 0%.<br>• The majority (96%) of the incremental benefits were accrued beyond the time points for which clinical data were available. The results from the cost-utility analysis are therefore highly uncertain, given the limited evidence around long-term effectiveness and the limitations in the health utility evidence. |

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RPE65 = retinal pigment epithelium 65 kDa protein.

## Conclusions

To address the identified limitations presented in Table 2, CADTH assumed a 10-year treatment duration for voretigene neparvovec, used data from crossover patients in Study 301 to inform short-term transition probabilities, and updated the sponsor's utility estimates with the values provided by clinical experts consulted by CADTH. The CADTH reanalysis of the sponsor's economic model estimated that the incremental cost-effectiveness ratio (ICER) for voretigene neparvovec compared with best supportive care (BSC) was $200,477 per quality-adjusted life-year (QALY) gained. To achieve an ICER of $50,000 per QALY compared with BSC, the price of voretigene neparvovec would need to be reduced by more than 74%.

The submitted price of voretigene neparvovec is a key driver of overall costs and of the ICER within the model. While the cost of voretigene neparvovec is known and is incurred at the beginning of the model time horizon, the majority (96%) of the clinical benefit (QALYs gained) was estimated through extrapolation beyond the observed trial period (Study 301). The extrapolations were made based on several assumptions with high levels of untestable uncertainty. Estimates for treatment effectiveness and natural history were further associated with both significant parameter and structural uncertainties.

Since the expected duration of the treatment effect of voretigene neparvovec and the utility estimates were also key drivers in the model, CADTH conducted additional scenario analyses that highlighted a wide range of plausible ICER estimates across different durations of treatment effect. Since most of the benefit estimated in the model originates from the improvements in quality of life as opposed to increased life expectancy, the results are sensitive to the choice of utility weights. Previous studies in different clinical settings

have shown that valuation of health states by proxies typically underestimates the utility weight in chronic disability health states compared with those elicited by the patients themselves. In such instances, this would overestimate differences in quality of life between voretigene neparvovec and BSC, which would result in a higher ICER for voretigene neparvovec. Together, these limitations indicate that the cost-effectiveness results should be cautiously interpreted.

## Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process.

The feedback for this review was provided jointly by Fighting Blindness Canada, the Canadian Council of the Blind, the Canadian National Institute for the Blind Foundation, and Vision Loss Rehabilitation Canada.

Patients or their caregivers described this disease as degenerative vision loss (the progressive loss of sight over time). They highlighted the challenges and impact of inherited retinal dystrophies (IRDs) on all aspects of life, including daily living, as well as physical and psychological challenges. This psychological strain is persistent and prolonged due to the progressive nature of IRDs. Patients also mentioned the negative impact on their employment status and on their family. Two-thirds of those surveyed reported their condition had negative effects on their families ranging from slightly negative to very negative.

No pharmacologic or surgical treatments were described in the patient group submission. Rather, a wide variety of modifications or aids such as canes, magnifiers, and specialized laptops were noted to be available to patients to navigate some of the day-to-day challenges of work and school. Only 1 individual noted experience with voretigene neparvovec. An informal interview was conducted by Fighting Blindness Canada staff with the parent of the child treated with voretigene neparvovec. The child had early symptoms of visual impairment at 2 months of age, with a confirmed diagnosis of Leber congenital amaurosis (LCA) with biallelic retinal pigment epithelium 65 kDa protein (RPE65) gene mutation made at 10 months based on a genetic test. Access to the treatment was provided as a special case following a request made to the government of Quebec, with both testing and treatment procedures reportedly streamlined and its associated costs covered. Prior to treatment, the child was light sensitive, had poor vision in dark and dim settings, and their vision was far from normal even during the day. Post-treatment results were almost immediately noticeable and led to an overall and extensive improvement in the child's confidence and self-reliance and relieved some of the complexities of caregiving. Although treatment did not lead to perfect vision and did not have any impact on visual acuity, the improvements were substantial compared with pre-treatment life. The parent was cognizant of the uncertain longevity of the drug, but still considered the treatment to provide invaluable benefits on quality of life due to the additional years of improved vision.

Genetic testing is an important factor in the diagnosis of underlying gene mutations and is an essential step in determining the appropriate treatment pathway for patients with IRDs. Among the survey respondents, more than one-third did not receive a genetic test or meet with a genetic counsellor, with most citing difficulty in getting tested, obtaining genetic counselling or receiving inconclusive results. The well-known shortage of genetic

counsellors and related infrastructure is a likely factor in the underutilization of genetic tests, illustrating an unmet need and an area for improvement in ocular treatment.

Several of these concerns were addressed in the sponsor's model:

- The sponsor captured the impact of IRD on quality of life through the application of utility weights. Utility weights were specific to each health state and elicited using the EuroQol 5-Dimensions (EQ-5D) instrument. The 5 domains in the EQ-5D (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) have the capability to capture the aforementioned impacts.
- The health states in the sponsor's model were defined to match the patients' description of disease progression. Specifically, peripheral and night vision were noted to be affected, with a progressive form of tunnel vision (narrowing of the visual field) occurring as the condition worsens. Health states that correspond to later stages of the disease (i.e., health state 4: counting fingers; health state 5: hand motion, light perception, and no light perception) were characterized by a loss of central vision and near or total blindness.
- The comparator in the model was BSC, defined as low-vision aids and supportive services related to medical vision care. This aligned with patients' experiences, in that no pharmacologic or surgical treatments have been previously available.
- A societal perspective that explored the impact of the condition and treatment with voretigene neparvovec on the patient's and caregiver's employment, as well as caregiver disutility, was explored in a scenario analysis.
- Furthermore, results of the sponsor's submission were consistent with the patient input in that most of the clinical benefits were attributed to improvements in quality of life as opposed to improvements in life expectancy.

# Economic Review

The current review is for voretigene neparvovec (Luxturna) for individuals with *RPE65*-mediated IRDs who have sufficient viable retinal cells.

## Economic Evaluation

### Summary of Sponsor's Economic Evaluation

*Overview*

The sponsor's economic evaluation compared voretigene neparvovec with BSC for the treatment of vision loss in patients with *RPE65*-mediated IRD who have sufficient viable retinal cells.[1] Sufficient viable retinal cells were defined based on Study 301 as an area of retina within the posterior pole with a thickness greater than 100 microns, as shown on optical coherence tomography (OCT), 3 or more disc areas of retina without atrophy or pigmentary degeneration within the posterior pole based on ophthalmoscopy, or a remaining visual field within 300° of fixation.[2] BSC was defined as low-vision aids and supportive services related to medical vision care.[1] The target population aligns with the Health Canada–indicated population and the sponsor's reimbursement request.

The recommended dose of voretigene neparvovec is $1.5 \times 10^{11}$ vector genomes (vg) administered by subretinal injection in each eye.[3] At the submitted price of $515,750 per injection (1 injection per eye), the 1-time cost is $1,031,500 per patient, assuming treatment in both eyes.[1] Because there are currently no treatments available for *RPE65*-mediated IRD

in Canada, the cost of BSC is dependent on an individual's use of visual aids and supportive services related to medical vision care.[1]

The clinical outcomes modelled were QALYs and blindness-free years.[1] In the base case, the sponsor's economic evaluation takes the perspective of a Canadian provincial public payer with a scenario analysis conducted from a societal perspective. The economic model was undertaken over a lifetime time horizon of 85 years (maximum age of 100 years) and used annual cycles with a discount rate of 1.5% applied to both health and cost outcomes.[1]

*Model Structure*

The economic evaluation was a 6-state Markov transition model with health states that capture visual health and mortality (Appendix 6, Figure 1).[1] Visual impairment was modelled based on a combination of visual acuity and visual field. The non–mortality related health states (from lower to higher visual impairment) were: moderate visual impairment (health state 1); severe visual impairment (health state 2); profound visual impairment (health state 3); counting fingers (health state 4); and hand motion, light perception to no light perception (health state 5) (Table 3).[1]

## Table 3: Definition of Modelled Health States Based on Worse of Visual Acuity or Visual Field

| | Worse of[a] | |
|---|---|---|
| **Health state** | **Visual acuity (LogMAR)** | **Visual field (°)** |
| 1: Moderate VI | < 1.0 | > 240 |
| 2: Severe VI | 1.0 to 1.4 | ≤ 240 and > 144 |
| 3: Profound VI | 1.4 to 1.8 | ≤ 144 and > 48 |
| 4: CF | > | ≤ 48 |
| 5: HM, LP, NLP | > 3.0 or an indication of HM, LP, or NLP | – |

CF = counting fingers; HM = hand motion; LogMAR = logarithm of the minimum angle of resolution; LP = light perception; NLP = no light perception; VI = visual impairment.

[a] Health states were defined based on the worse of either the visual acuity or the visual field criteria.

The model begins with a cohort of individuals with *RPE65*-mediated IRD distributed across the vision-related health states as per Study 301.[1] During the initial phase (1 year in length), individuals' vision may improve (e.g., transition from health state 2 to health state 1), remain the same (i.e., stay in their initial health state), or decline (e.g., transition from health state 2 to health state 3). Following the initial phase, individuals treated with voretigene neparvovec enter the stabilization phase. In this phase, an individual's vision cannot decline. The duration of the stabilization phase was assumed to be 40 years. Following the initial phase, individuals treated with BSC and after the stabilization phase for individuals who received voretigene neparvovec, individuals in both arms enter the long-term phase where vision can decline. Patients could transition from any of these states to the absorbing death state.[1]

*Model Inputs*

Baseline patient characteristics were sourced from Study 301, an open-label, randomized control trial.[2] Patients entered the model at 15.1 years of age and 42% were male. Dosing was consistent with the product monograph and it was assumed that patients would receive voretigene neparvovec once per eye over their lifetime.[1]

The transition probabilities between health states in both the voretigene neparvovec and BSC arms for the initial phase of the model were informed by the outcomes reported at the

1-year follow-up in Study 301.[2] The length of the stabilization phase, where individuals in the voretigene neparvovec arm do not observe a change in vision, was assumed to be 40 years based on clinical guidance and scientific rationale.[1] Disease progression in the long-term phase was informed by data from the RPE65 NHx study, a sponsor-commissioned retrospective chart review of 70 patients with retinal degenerative disease and confirmed biallelic mutations in the *RPE65* gene with a mean follow-up duration of 7.28 years.[4] Parametric multistate models (MSMs) were fitted to estimate the decline in vision status over time, with a Weibull distribution selected based on model fit.[1] The amount of vision decline in the voretigene neparvovec arm (i.e., probability of progressing to a worse health state) was assumed to be reduced by 25% based on the assumption that 25% of the retina would be treated with voretigene neparvovec and the rate of decline would be similarly reduced.[1]

Age-specific general population life tables were used, with increased mortality risk applied based on the individual's current vision health state.[1] The increased mortality risk due to the patient's visual impairment state was sourced from a study on individuals aged 64 to 84 years and applied in the model across all ages.[5]

Patients accrued health state–specific costs and QALYs and treatment-related costs as they transitioned through the health states in the model.[1] Health state utilities were sourced from a sponsor-commissioned utility study in which 6 retina specialists assessed a series of health state vignettes and assigned an impact on health-related quality of life using the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L).[6] Canadian tariffs were applied to the EQ-5D-5L scores as described in a study by Xie et al.[7]

Modelled adverse events included cataract, eye inflammation, and increased intraocular pressure in which there were both utility decrements and cost impacts. Study 301 informed the proportion of patients experiencing each adverse event with disutilities applied based on the event's expected duration and the utility decrement based on a literature review.[1]

The model included the cost of acquisition, administration, and monitoring associated with voretigene neparvovec. Furthermore, the cost of genetic testing to identify, among all IRD patients, those who have an *RPE65* mutation, and the cost of OCT testing to determine eligibility among those with *RPE65*-mediated IRD patients, were included.[1] In addition, health care resource use was included, broken down into 5 categories: hospitalization, vision care and costs, visual assistance and aids, residential care, and community care. Hospitalization, vision care and costs, and visual assistance and aids were stratified by age categories (school age [< 18 years], working age [18 to 65 years], and retirement age [> 65 years]), while residential and community care applied only to those at retirement age.[1] Health care resource utilization unit costs were sourced mainly from Canadian public payer sources but, in the absence of Canadian data, publications from a variety of international jurisdictions were utilized.

## Summary of Sponsor's Economic Evaluation Results

All probabilistic analyses presented subsequently were based on 10,000 iterations. The probabilistic and deterministic results were comparable.

### *Base Case Results*

The sponsor's base case comprised the Health Canada–indicated population. Voretigene neparvovec was associated with incremental costs of $951,878 and incremental QALYs of 9.2, resulting in an incremental cost-effectiveness ratio (ICER) of $103,075 per QALY compared with BSC (Table 4). The results were primarily driven by drug acquisition and

administration costs, and costs related to health care resource use (see Table 11 in Appendix 3 for disaggregated costs). QALY gains associated with voretigene neparvovec were largely driven by the additional time spent in the least severe health state (see Table 11 in Appendix 3 for disaggregated QALYs). At a willingness-to-pay threshold of $50,000 per QALY, the probability of voretigene neparvovec being cost-effective was 0%; at a willingness-to-pay threshold of $100,000 per QALY, the probability of voretigene neparvovec being cost-effective was 53.3% (Figure 2 and Figure 3).

## Table 4: Summary of the Sponsor's Economic Evaluation Results

| Drug | Total costs ($) | Incremental costs ($) | Total QALYs | Incremental QALYs | ICER versus BSC ($/QALY) |
|---|---|---|---|---|---|
| BSC | 308,914 | – | 18.4 | – | – |
| Voretigene neparvovec | 1,260,792 | 951,878 | 27.6 | 9.2 | 103,075 |

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[1]

Additional figures and base case results from the sponsor's submitted economic evaluation are presented in Figure 2 to Figure 5 in Appendix 3 (including the cost-effectiveness acceptability curve, the cost-effectiveness plane, and the change in vision status over time).

### *Sensitivity and Scenario Analysis Results*

The sponsor conducted both deterministic 1-way sensitivity and scenario analyses (results of the scenario analyses are presented in Table 12 in Appendix 3).

The model was most sensitive to the discount rate, the expected duration of treatment effect, and adopting a societal perspective. Changing the duration of the stabilization phase (i.e., treatment effect duration for voretigene neparvovec) to 20 years resulted in an ICER of $138,299 per QALY, a 47% increase from the sponsor's base case. Furthermore, from a societal perspective, the ICER decreased to $33,570 per QALY, a 64% decrease from the sponsor's base case.

## CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis:

- **Limited evidence on the durability of the treatment effect of voretigene neparvovec:** There is limited evidence surrounding the expected duration of the treatment effect. The sponsor assumed within the submitted model that the duration of treatment effects would be 40 years, justifying this to be the midpoint between the maximum available follow-up (7.5 years) and the remaining expected lifetime of patients treated with voretigene neparvovec (70 years). Although the phase I study, Study 101, provides a maximum of 7.5 years of follow-up, this was a dose-escalation study with different eligibility criteria for defining sufficient viable retinal cells. Results from this study may not be generalized to the dose submitted to Health Canada for approval and evaluated in Study 301. Clinical experts consulted by CADTH indicated that a 40-year treatment effect is likely to be an overestimation of the expected duration.[8] The durability of the treatment effect informed the stabilization phase, and a longer treatment effect duration meant that patients maintain their year 1 outcomes longer. As such, this is likely to bias cost-effectiveness estimates in favour of voretigene neparvovec as QALY gains are extended.

- CADTH adopted a more conservative treatment effect duration, setting it to 10 years for the CADTH base case. In recognition that the duration of treatment effect is uncertain, additional sensitivity analyses were conducted, varying the durations to 15 years and 20 years.

- **Methodological issues with the approach used to model natural history:** To inform the natural history of the condition, the sponsor commissioned the RPE65 NHx study, a retrospective chart review of 70 patients with retinal degenerative disease and confirmed biallelic mutations in the *RPE65* gene.[4] In response to a request for additional information, the sponsor informed CADTH that approximately 80% of the observations in the RPE65 NHx study were missing a visual field measurement. To handle this missing data, a last observation carried forward approach was taken in which patients with missing data were assigned a health state by imputing (carrying forward) a previous observation or, if a previous observation was not available, the health state was assigned using only visual acuity. Due to the progressive nature of the disease, this imputation method is inappropriate and is likely to underestimate downward disease progression. The clinical experts consulted by CADTH further noted that visual acuity and visual field may not always be correlated; thus, it would be difficult to assign one based on the other, as was done by the sponsor. It is also unclear if the visual field measurements were missing completely at random or not.

  With the patient-level data, the sponsor then fitted parametric MSMs with different statistical distributions to estimate how vision status would decline over time. When estimating this MSM, the sponsor enforced progression by eliminating data points that indicated "improvement" (i.e., patients were not allowed to "improve" health states between visits). This is not appropriate, even in the case of a progressive disease, as chance and measurement error would imply there will be some random variation over time whereby vision status could be measured to improve. By removing the "improved" data points from the analysis, the disease would be modelled as more progressive than in reality.

  - Based on a request for additional information, the sponsor provided the MSM estimates that excluded the imputed data. CADTH conducted a scenario analysis using the revised MSM estimates. CADTH was unable to address the limitations regarding forced progression and missingness at random as part of the reanalysis. Given that BSC patients enter the long-term phase after the initial year (i.e., 1 year in duration), whereas patients receiving voretigene neparvovec are modelled by this data only after both the initial and stabilization phase, the potential biases introduced from the use of the RPE65 NHx study would be expected to have a larger impact on the extrapolation to the BSC group.

- **Uncertainty in the comparative efficacy information:** Comparative treatment efficacy in the initial phase of the model was informed by Study 301 and considered only the randomized patient population. Study 301 was an open-label trial and, as such, patient and researcher awareness of treatment allocation may affect the evaluation of patient-reported outcomes, especially the reporting of adverse events. The sample size within this trial (N = 31) was small and imbalances in baseline characteristics between the voretigene neparvovec group and the control group introduced a potential risk of bias. Due to the study's small sample size, estimates of the transition probability matrices were highly unstable or even impossible, since several transitions had no observations. For instance, no data were available from Study 301 to inform transitions starting from health state 5. To account for these missing transitions, the sponsor assumed that patients in health state 5 would transition to the different health states in the exact same manner as those in health state 4 (i.e., if all patients in health state 4 transitioned to health state 3, it was assumed all patients in health state 5 would transition to health state 4). This is inappropriate, as the transition probabilities are not likely to be consistent across health states as assumed. The sparsely estimated transition probability matrices resulted in high uncertainty on the treatment effect estimates.

The sponsor's base case further omitted data from patients who crossed over from the control group to the voretigene neparvovec group in Study 301 at year 1 (n = 9). Even though the rationale to omit these patients was that the treatment estimates for voretigene neparvovec no longer reflected a randomized comparison, the small sample size in the trial meant that outcomes in a few patients could have a substantial impact on results.

Of note, the trial's primary end point, the multi-luminance mobility test (MLMT), could not be used for the cost-effectiveness analysis, as there was limited information surrounding this novel end point. No data were available linking this outcome to costs, utilities, or mortality, and no data were available on the long-term changes in this outcome.

- Given the already small sample size and existing imbalances at baseline in Study 301 that are noted in the CADTH Clinical Review Report, CADTH included the data for all patients who received the labelled dose of voretigene neparvovec, including those who were originally included in the control arm of Study 301, to inform the treatment estimates of voretigene neparvovec.

- **Use of physician proxies to inform utility weights:** The utilities used in the model were not sourced from the general population or from the patient population studied directly in the trial. Rather, they were elicited from 6 clinicians who were presented with vignettes (health state descriptions) and who then assigned utilities based on the EQ-5D-5L questionnaire.[6] Given the small sample size and the fact that uncertainty estimates in the model do not appropriately capture the methodological uncertainty of using clinician proxies, the sponsor's approach may not accurately reflect the health state utilities for this population.
  - CADTH considered this strategy suboptimal, but acknowledged that few options are available to derive utility weights. The clinical experts consulted by CADTH were asked to complete the utility elicitation exercise in which the results were then incorporated into the sponsor's existing utility estimates. The addition of the CADTH clinical experts' results, on average, resulted in similar utility scores, but with a much larger variance. Furthermore, CADTH conducted a scenario analysis using Health Utility Index Mark 3 estimates to address potential methodological uncertainty in the use of different measurement tools to convert utility weights.
- **Concerns with the MSM model:** As mentioned previously, the natural history of the condition was informed by fitting an MSM to the RPE65 NHx study data. The modelling technique used in the sponsor's MSM assumed that the probability of transitioning from 1 health state to another would be dependent on an individual's current health state and the time since model start (i.e., a clock-forward approach).[9] This approach may not be appropriate in the context of a Markov cohort model, since patients in the RPE65 NHx study do not start in the initial health state modelled.[10] Alternatively, the MSM could have been estimated so that transition probabilities were dependent on an individual's current health state and on how long they have occupied that particular state (clock-reset approach). The sponsor did not provide recommended diagnostic results on why a clock-forward approach was more suited than a clock-reset approach. This limitation may have an impact on parameter estimates as well as the best fitting distribution and, by extension, on the outcomes extrapolated within the cost-utility analysis.
  - CADTH was unable to address this limitation, given that the correct use of an MSM would have required having patient-level data to understand whether the probability of transitioning from 1 state to another was dependent on how long an individual had been in a particular health state. It would further require a different modelling specification (e.g., individual-level decision model microsimulation).

One additional limitation was identified but was considered unlikely to change or to heavily impact the analyses. This limitation is outlined subsequently.

- **Adverse events applied to the initial year:** The submitted model assumed an adverse event could occur only in the first year after the index procedure and excluded the serious adverse events that occurred in only 1 patient in Study 301. The clinical experts consulted by CADTH expressed discomfort with this decision. The combined safety evidence from Study 301 and from phase I trials indicated that some surgery-related adverse events could lead to chronic side effects and permanent vision loss (endophthalmitis and foveal thinning). This is particularly concerning because failing to consider late, isolated adverse events that lead to permanent vision loss would therefore not account for their effects on health utilities and costs within the decision model.[11]

## Table 5: Key Assumptions of the Submitted Economic Evaluation

| Sponsor's key assumption | CADTH comment |
|---|---|
| Those with normal vision would be included in the moderate visual impairment health state (i.e., HS1). Blindness, and its associated implications, was defined as HS2 to HS5. | Appropriate. |
| Visual impairment is associated with an increased risk of mortality, as informed by the literature.[5] The source for the mortality increase was a study on individuals aged 64 to 84. | Some of the clinical experts consulted by CADTH noted that the population from which these data were sourced was older and likely did not reflect the comorbidity profile of those receiving VN. However, most experts agreed there would be an added risk of mortality for this patient population compared with the general population. The true risk increase in mortality is currently unknown but thought to lie probably somewhere in between. |
| In the first year (i.e., initial phase of the model), individuals in both treatment arms could move to better or worse health states. | Reasonable. This reflects the trial evidence. |
| The analysis of the clinical data from Study 301 that informed the transitions in the initial phase of the model relied on a modified intention-to-treat analysis. | Appropriate. Unlikely to bias the results. |
| All patients with retinal dystrophy will undergo genetic testing. Genetic testing is applied to the full patient population and not only to the patients who receive VN (by inflating the cost of testing to include those with identified confirmed biallelic *RPE65* mutations). | Appropriate and likely conservative. Feedback from provincial drug plans suggests it is currently not standard practice for all jurisdictions to reimburse for genetic testing. |

HS = health state; RPE65 = retinal pigment epithelium 65 kDa protein; VN = voretigene neparvovec.

## CADTH Reanalyses of the Economic Evaluation

### *Base Case Results*

CADTH undertook the reanalyses that are outlined in Table 6 in an effort to address the limitations within the model. CADTH was not able to fully address the limitations related to the estimation and application of the MSM, the uncertainty in the comparative efficacy estimates, or the utility estimates.

## Table 6: CADTH Revisions to the Submitted Economic Evaluation

| Stepped analysis | Sponsor's value or assumption | CADTH value or assumption |
|---|---|---|
| **Corrections to sponsor's base case** | | |
| None | | |
| **Changes to derive the CADTH base case** | | |
| 1. Duration of treatment effect | 40 years | 10 years |
| 2. Limited clinical evidence due to small sample size | Data from the control arm patients who received the study treatment at 1 year were not incorporated to inform transition probabilities for VN | Data from the control arm patients who received the study treatment at 1 year were included in the analysis (i.e., crossover data were included) |
| 3. Utility estimates were sourced from a small number of clinical experts | Health states and utility values, mean (SD):<br>• HS1: mean = 0.78 (SD = 0.07)<br>• HS2: mean = 0.66 (SD = 0.03)<br>• HS3: mean = 0.52 (SD = 0.07)<br>• HS4: mean = 0.38 (SD = 0.06)<br>• HS5: mean = 0.30 (SD = 0.08) | Clinical experts consulted by CADTH completed the sponsor's utility elicitation exercise. CADTH pooled these utility estimates with the sponsor's data. Pooled utility estimates:<br>• HS1: mean = 0.80 (SD = 0.07)<br>• HS2: mean = 0.68 (SD = 0.07)<br>• HS3: mean = 0.51 (SD = 0.18)<br>• HS4: mean = 0.36 (SD = 0.19)<br>• HS5: mean = 0.26 (SD = 0.21) |
| CADTH base case | Combined revisions (1 + 2 + 3) | |

HS = health state; SD = standard deviation; VN = voretigene neparvovec.

CADTH applied each change listed in Table 6 to the sponsor's base case and the effect of each individual change can be found in Table 7. The cumulative effect of all the changes is also reported in Table 7.

The CADTH reanalysis resulted in voretigene neparvovec generating $1,019,882 in additional costs and 5.09 additional QALYs when compared with BSC. The ICER for voretigene neparvovec compared with BSC was $200,477 per additional QALY. The probability of voretigene neparvovec being cost-effective is 0% and 1% at a willingness-to-pay threshold of $50,000 per QALY and $100,000 per QALY, respectively. Approximately 4% of the incremental QALY benefits associated with voretigene neparvovec occurred in the first 5 years after treatment (the maximum follow-up duration of Study 301). CADTH found that the largest driver of cost and health outcomes was the duration of the voretigene neparvovec treatment effect. Modifying the length of the voretigene neparvovec treatment effect from 40 to 10 years (reanalysis 1) resulted in a 202% increase in the ICER estimates. The inclusion of pooled utility estimates (reanalysis 3) resulted in a 14% reduction in the ICER estimates, as higher utility weights were estimated in health states where voretigene neparvovec patients have a longer time in the health state (i.e., health states 1 and 2), and a lower utility weight for health states in which BSC patients spent more time. The disaggregated results are presented in Table 13 in Appendix 4.

## Table 7: Summary of the Stepped Analysis of the CADTH Reanalysis Results

| Stepped analysis | Treatment | Total costs ($) | Total QALYs | ICER ($/QALYs) |
|---|---|---|---|---|
| Sponsor's base case | BSC | 308,914 | 18.38 | – |
| | VN | 1,260,792 | 27.61 | 103,075 |
| CADTH reanalysis 1 | BSC | 309,209 | 18.32 | – |
| | VN | 1,321,784 | 22.93 | 219,647 |
| CADTH reanalysis 2 | BSC | 309,444 | 18.31 | – |
| | VN | 1,275,027 | 27.33 | 107,049 |
| CADTH reanalysis 3 | BSC | 309,207 | 17.51 | – |
| | VN | 1,260,479 | 28.12 | 89,743 |
| CADTH base case | BSC | 308,932 | 17.60 | – |
| | VN | 1,328,815 | 22.69 | 200,477 |

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; VN = voretigene neparvovec.

### *Scenario Analysis Results*

CADTH performed several scenario analyses on the CADTH base case. These analyses included:

- assuming a different duration of treatment effect
- basing utility estimates on the Health Utility Index
- excluding the cost of genetic testing
- excluding the cost of visual aids and/or residential and community care
- assuming no increased mortality risk due to blindness
- adopting a societal perspective
- excluding crossover trial data
- using MSM estimates fitted on non-imputed data
- removing the 25% relative risk reduction in vision deterioration after the treatment effect of voretigene neparvovec has ended.

Results of these scenario analyses are presented in Table 14 in Appendix 4.

Adopting a societal perspective that captured caregiver disutility and the costs of non–health care resources had the largest impact by lowering the incremental costs to $790,441, with little impact on incremental QALYs (i.e., 5.08 QALYs). The resulting ICER of voretigene neparvovec compared with BSC decreased by 22% to $155,714 per QALY. The disaggregated results of the societal perspective analysis are presented in Table 16 in Appendix 4. As noted previously, the sponsor's model was noted to be sensitive to the assumption on the duration of the voretigene neparvovec treatment effect. Doubling the durability of the expected treatment effect from 10 years to 20 years resulted in a 31% decrease in the ICER compared with the CADTH base case. CADTH also undertook an additional exploratory analysis to present estimates on the effect of the possibility of re-treatment, as raised by clinical experts consulted by CADTH. The results of this exploratory analysis are presented in Table 14 in Appendix 4.

CADTH applied a series of price-reduction analyses to both the sponsor's base case and CADTH's base case. Results from these analyses can be found in Table 8. To achieve an

ICER below $50,000 per QALY, a price reduction of 74% would be required; to achieve an ICER below $100,000 per QALY, a price reduction of 49% to the CADTH base case would be required.

## Table 8: CADTH Price-Reduction Analyses

| | ICERs for VN versus BSC | |
|---|---|---|
| **Price reduction** | **Sponsor base case ($)** | **CADTH reanalysis ($)** |
| No price reduction | 103,075 | 200,477 |
| 10% | 91,561 | 180,130 |
| 20% | 80,453 | 159,784 |
| 30% | 69,661 | 139,438 |
| 40% | 58,358 | 119,091 |
| 50% | 46,824 | 98,745 |
| 60% | 35,966 | 78,399 |
| 70% | 24,615 | 58,052 |
| 80% | 13,407 | 37,706 |

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; VN = voretigene neparvovec.

## Issues for Consideration

- As noted in the CADTH Clinical Review Report, the clinical experts consulted by CADTH noted there is no objective clinical definition of sufficient viable retinal cells. Yet, the indication for voretigene neparvovec within the product monograph stipulates that patients must have sufficient viable retinal cells.[12] According to the clinical experts consulted, the methods used in the pivotal trial to determine whether a patient had sufficient viable retinal cells does not give a complete picture of the health of the retina or the number of viable photoreceptors. Rather, the definition of sufficient retinal cells may be patient-specific and there may not be an objective measure. In real-world practice, the definition may be implemented based on OCT examinations that would be supplemented by tests of visual acuity and visual function. Adopting a different and potentially broader definition would be expected to have an impact on the patient population eligible for voretigene neparvovec and the expected budget impact.
- With the availability of voretigene neparvovec, the first few years of its implementation would most likely treat a prevalent population with similar patient characteristics as those in Study 301. According to the clinical experts consulted by CADTH, over time, the eligible population to be treated with voretigene neparvovec will shift to reflect a greater proportion of incident cases where patients might present younger and with less severe disease at baseline. Although the CADTH Clinical Review Report identified a subgroup analysis based on age (< 18 years at first injection versus ≥ 18 years at first injection) that was conducted by the sponsor, this was a post hoc analysis that should be considered hypothesis-generating. Furthermore, while patient age can be used as a proxy to estimate how advanced the condition is, *RPE65* mutation–associated retinal dystrophy is a heterogeneous condition with differences in the age of onset and disease progression. The clinical experts consulted by CADTH indicated that greater clinical benefit from treatment is expected earlier in the condition when there are more viable retinal cells for the gene replacement therapy to restore. No subgroup analysis was identified based on retinal cell viability within the clinical review. It remains unclear if the cost-effectiveness of voretigene neparvovec might differ in less severe patients, given the lack of available clinical subgroup data.
- Although there are no other pharmacological treatment options available for IRD, retinal prosthetic devices such as the Argus II Retinal Prosthesis System have been used in

these patients to manage their condition. In fact, some Canadian health technology assessment agencies, such as Health Quality Ontario, have conducted health technology assessments on this technology.[13] According to the clinical experts consulted by CADTH, the Argus device has since been withdrawn by the sponsor from the Canadian marketplace and, therefore, the exclusion of this device as a comparator in the analysis is appropriate. The clinical experts further noted that Argus is developing another, similar device but its role and use in patients with IRD remains unclear.

- The Health Canada–approved indication notes that disease-causing biallelic *RPE65* mutations should be confirmed by an accredited laboratory using validated assay methods.[12] The drug plans consulted by CADTH noted variability in the access and reimbursement of genetic testing to confirm biallelic *RPE65* mutations across jurisdictions. Most jurisdictions noted that genetic testing was not available locally, with testing accessed by sending samples out of the province or out of the country. Though the clinical experts consulted for this review raised no concern regarding the availability of genetic tests, the approach to funding is heterogeneous by jurisdiction (e.g., ministerial, or local laboratory or hospital budget). Both the sponsor's and CADTH's base case assumed genetic testing would be covered publicly. To evaluate the impact of these costs on the overall cost-effectiveness of voretigene neparvovec, CADTH further conducted a scenario analysis that assumed these costs would not be covered by a public payer.
- The sponsor's model assumed treatment is given only once in a patient's lifetime. However, some clinical experts consulted by CADTH noted a potential role for re-treatment with voretigene neparvovec after the initial treatment effect has waned. The role of re-treatment is uncertain at this time, given there is no evidence on either the efficacy or safety of re-treatment. If re-treatment is possible, this would affect the cost-effectiveness estimates of voretigene neparvovec. To assess this potential impact, CADTH conducted an exploratory analysis assuming half of the patients would be re-treated at year 10.

## Overall Conclusions

To address the identified limitations, CADTH assumed a 10-year treatment duration for voretigene neparvovec, used data from crossover patients in Study 301 to inform short-term transition probabilities, and pooled the sponsor's utility estimates with the values provided by the clinical experts consulted by CADTH. CADTH's reanalysis of the sponsor's economic model estimated that the ICER of voretigene neparvovec compared with BSC was $200,477 per QALY gained. To achieve an ICER of $50,000 per QALY compared with BSC, the price of voretigene neparvovec would need to be reduced by more than 74%.

The submitted price of voretigene neparvovec is 1 of the key drivers of overall costs and of the ICER within the model. While the cost of voretigene neparvovec is known and is incurred at the beginning of the model time horizon, the majority (96%) of the clinical benefit (QALYs gained) was estimated through extrapolation beyond the observed trial period (Study 301). The extrapolations were made based on several assumptions with high levels of untestable uncertainty. The clinical estimates for treatment effectiveness and natural history were further associated with both significant parameter and structural uncertainties. The clinical data from Study 301 and the RPE65 NHx study that informed the economic model inputs were highly heterogeneous and based on small samples that introduce greater imprecision. In addition, the effectiveness data were immature and methodological limitations exist around incorporating the estimates from the MSM into the economic model to inform the natural history of the condition. CADTH was not able to adjust the economic model to correctly accommodate the MSM estimates. Furthermore, CADTH noted methodological issues with the MSM data (e.g., high degree of missing values, approach used to handle

missing data, and assumptions of progressiveness), and the magnitude and direction of the bias introduced by these issues remains unclear.

There were several other key drivers to the model, including the duration of the treatment effect of voretigene neparvovec and the utility estimates. Scenario analyses conducted by CADTH highlighted the broad range of plausible ICER estimates across different assumed durations of treatment effect. However, the short follow-up duration for patients treated with voretigene neparvovec makes it difficult to directly estimate an expected duration of treatment effect, and this uncertainty is carried through into the ICER estimate. Since most of the benefit estimated by the model originates from the improvements in quality of life as opposed to increased life expectancy, the results are sensitive to the choice of utility weights. The estimation of the utility weights was noted by CADTH as a key limitation, given that the sponsor elicited them from physician proxies as opposed to patients or members of the public. Alternative values would be expected to have a significant impact on the outcomes. The valuations of health states by proxies in previous studies in different clinical settings have indicated that proxies typically underestimate the utility weight in chronic disability health states compared with patients themselves and, in such instances, would overestimate the differences in quality of life between voretigene neparvovec and BSC. As such, the ICER is highly uncertain; if the utility weights of more severe health states are underestimated, this would result in a higher ICER for voretigene neparvovec. Together, these limitations indicate that the cost-effectiveness results should be cautiously interpreted.

# Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and, as such, the table may not represent the actual costs to public drug plans.

## Table 9: CADTH Cost Comparison Table for *RPE65*-Mediated Inherited Retinal Dystrophy

| Treatment | Strength | Form | Price ($) | Recommended dosage | Course cost ($)[a] |
|---|---|---|---|---|---|
| Voretigene neparvovec (Luxturna) | $5 \times 10^{12}$ vg/mL | Concentrate | 515,750.0000[b] | $1.5 \times 10^{11}$ vg per eye, administered by subretinal injection | 1,031,500 |

RPE65 = retinal pigment epithelium 65 kDa protein; vg = vector genomes.

[a] The course cost is the cost per patient for both eyes.

[b] Sponsor-provided price. The price is per injection for each eye.

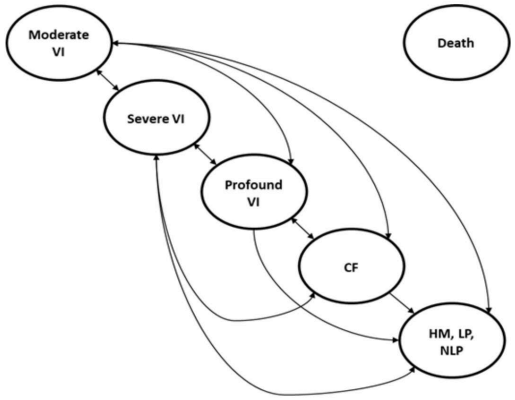
# Appendix 2: Submission Quality

## Table 10: Submission Quality

| Description | Yes | No | Comments |
|---|---|---|---|
| Population is relevant, with no critical intervention missing and no relevant outcome missing. | ☒ | ☐ | Although life-years were not reported as an outcome to the model, the intervention is expected to have very minor impacts on overall life expectancy. |
| Model has been adequately programmed and has sufficient face validity. | ☒ | ☐ | |
| Model structure is adequate for the decision problem. | ☒ | ☐ | |
| Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis). | ☒ | ☐ | |
| Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem. | ☐ | ☒ | The parameter uncertainty was adequately addressed. There is structural uncertainty that could not be adequately explored. Utility estimates may not capture the uncertainties associated with expert-elicited utilities.<br><br>The model also did not adequately capture the impact of missing or imputed data, nor did the submission adequately characterize the magnitude of the missingness. The model does not consider the uncertainty related to whether the natural history of the disease justifies a clock-forward approach for estimating the multistate model. |
| The submission was well organized and complete; the information was easy to locate (clear and transparent reporting, technical documentation available in enough details). | ☒ | ☐ | The submission overall is well organized, but the implementation of using multistate model coefficients to generate transition probabilities could use further documentation. CADTH sent out requests for additional information to better understand the multistate model; in all cases, the sponsor responded to CADTH's requests. |

# Appendix 3: Additional Information on the Submitted Economic Evaluation

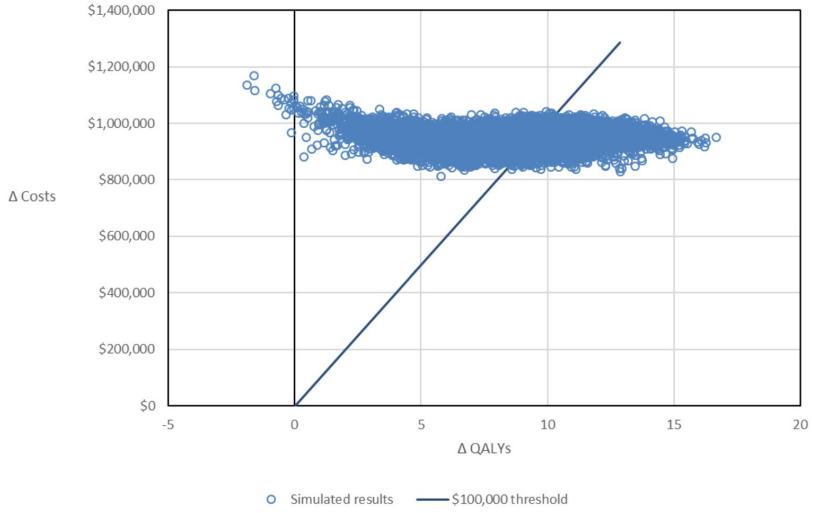
## Figure 1: Model Structure




CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception; VI = visual impairment.

Source: Sponsor's pharmacoeconomic submission.[1]

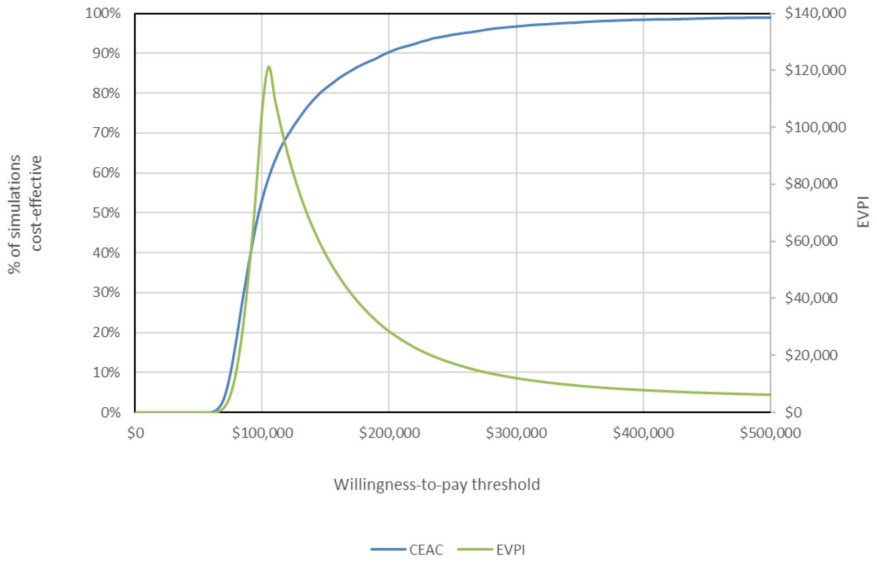
## Figure 2: Cost-Effectiveness Plane




QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[1]

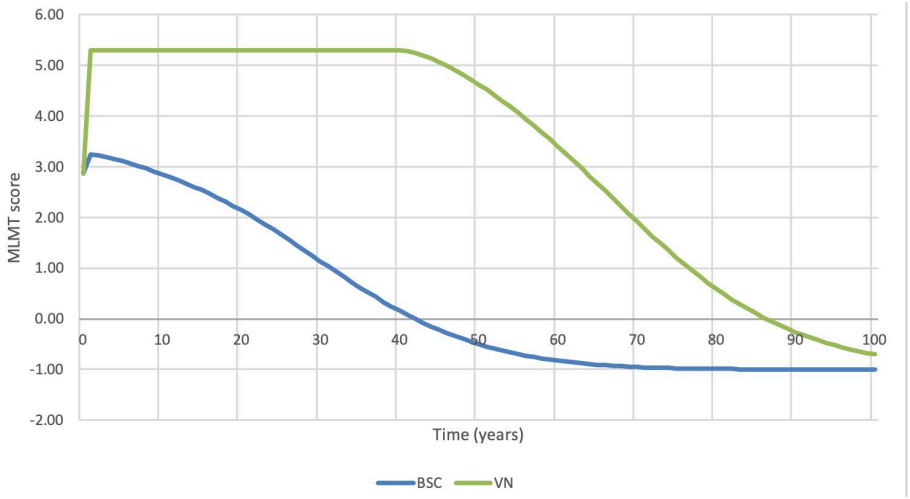
## Figure 3: Cost-Effectiveness Acceptability Curve and Expected Value of Perfect Information




CEAC = cost-effectiveness acceptability curve; EVPI = expected value of perfect information.

Source: Sponsor's pharmacoeconomic submission.[1]

## Figure 4: Change in MLMT Score Over Time, by Treatment Group

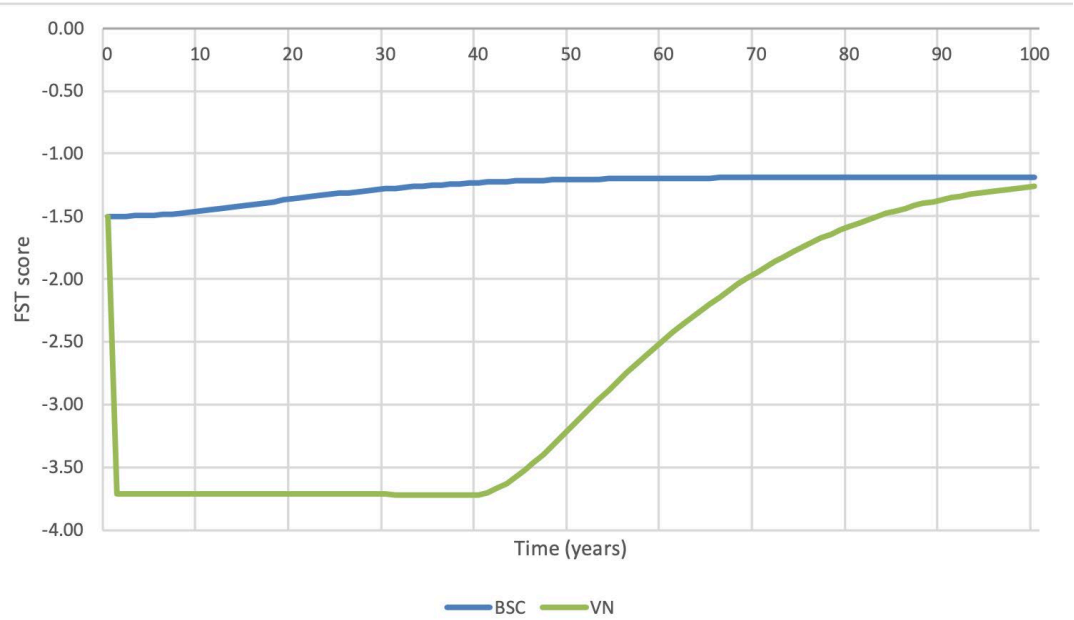



BSC = best supportive care; MLMT = multi-luminance mobility test; VN = voretigene neparvovec.

NOTE: Higher MLMT score indicates improved functional vision.

Source: Sponsor's pharmacoeconomic submission.[1]

## Figure 5: Change in FST Over Time, by Treatment Group




BSC = best supportive care; FST = full-field light sensitivity threshold; VN = voretigene neparvovec.

NOTE: Lower FST score indicates improved light sensitivity.

Source: Sponsor's pharmacoeconomic submission.[1]

## Table 11: Disaggregated QALYs and Costs, 2019 CA$

| Parameter | VN | BSC | Incremental |
|---|---|---|---|
| **Discounted QALYs** | | | |
| Total | 27.6 | 18.4 | 9.2 |
| Health state 1 | 18.8 | 3.0 | 15.8 |
| Health state 2 | 5.0 | 2.9 | 2.1 |
| Health state 3 | 1.8 | 5.0 | −3.2 |
| Health state 4 | 1.2 | 2.3 | −1.1 |
| Health state 5 | 0.9 | 5.2 | −4.3 |
| Adverse event disutility | −0.01 | 0 | −0.01 |
| Caregiver disutility | 0 | 0 | 0 |
| **Discounted costs ($)** | | | |
| Total | 1,260,792 | 308,914 | 951,878 |
| Voretigene neparvovec | 1,035,079 | 0 | 1,035,079 |
| Eligibility testing | 32,737 | 0 | 32,737 |
| Adverse events | 770 | 0 | 770 |
| Total health care resource use | 192,206 | 308,914 | −116,708 |
| Hospitalization | 25,488 | 49,812 | −24,324 |
| General ophthalmic services | 83,643 | 163,623 | −79,980 |
| Vision assistance and aids | 28,759 | 28,509 | 250 |

| Parameter | VN | BSC | Incremental |
|---|---|---|---|
| Residential care | 50,854 | 62,696 | −11,843 |
| Community care | 3,463 | 4,273 | −811 |
| Non–health care resource use | 0 | 0 | 0 |
| Home modifications | 0 | 0 | 0 |
| ICER ($/QALY) | 103,075 | | |

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

## Table 12: Sponsor-Submitted Scenario Analyses

| Parameter or assumption | Incremental costs ($) | Incremental QALYs | ICER ($ per QALY) | Percentage change from base case, ICER |
|---|---|---|---|---|
| Base case | 952,433 | 10.13 | 93,979 | 0% |
| Societal perspective (including caregiver disutilities) | 367,673 | 10.95 | 33,570 | −64% |
| Discount rate for costs and outcomes: 3% | 987,607 | 6.59 | 149,788 | 59% |
| Discount rate for costs and outcomes: 0% | 891,374 | 16.7 | 53,368 | −43% |
| Duration of treatment effect: 20 years | 999,116 | 7.22 | 138,299 | 47% |
| Duration of treatment effect: 30 years | 978,510 | 8.9 | 110,003 | 17% |
| Duration of treatment effect: Lifetime | 867,173 | 11.61 | 74,702 | −21% |
| Utility values: Brown[14] | 952,433 | 7.93 | 120,097 | 28% |

HS = health state; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

# Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

## Detailed Results of the CADTH Base Case

### Table 13: Disaggregated Summary of CADTH's Economic Evaluation Results (Ministry of Health Perspective)

| Parameter | VN | BSC | Incremental | Percentage (of total incremental) (%) |
|---|---|---|---|---|
| | **Discounted QALYs** | | | |
| **Total** | **22.69** | **17.60** | **5.09** | **100** |
| Health state 1 | 10.17 | 3.10 | 7.07 | 139 |
| Health state 2 | 5.48 | 2.99 | 2.48 | 49 |
| Health state 3 | 2.76 | 4.85 | −2.09 | −41 |
| Health state 4 | 1.51 | 2.18 | −0.67 | −13 |
| Health state 5 | 2.79 | 4.47 | −1.69 | −33 |
| Adverse event disutility | −0.01 | 0.00 | −0.01 | 0 |
| | **Discounted costs ($)** | | | |
| **Total** | **1,328,815** | **308,932** | **1,019,882** | **100** |
| Voretigene neparvovec | 1,035,081 | 0 | 1,035,081 | 101 |
| Eligibility testing | 32,785 | 0 | 32,785 | 3 |
| Adverse events | 769 | 0 | 769 | 0 |
| Health care resource use | 260,180 | 308,932 | −48,753 | −5 |
| Hospitalization | 39,451 | 49,900 | −10,449 | −1 |
| General ophthalmic services | 129,444 | 163,776 | −34,332 | −3 |
| Vision assistance and aids | 28,613 | 28,475 | 138 | 0 |
| Residential care | 58,671 | 62,519 | −3,849 | 0 |
| Community care | 4,000 | 4,261 | −261 | 0 |
| ICER ($/QALY) | 200,476.00 | | | |

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

## Scenario and Exploratory Analyses

Scenario analyses performed on the CADTH base case included: assuming different durations of treatment effect (i.e., 15 years and 20 years), utility estimates based on the Health Utility Index, excluding the cost of genetic testing, excluding the cost of visual aids and/or residential and community care, assuming no increased mortality risk due to blindness, adopting a societal perspective, excluding crossover trial data, and using MSM estimates fitted on non-imputed data.

In scenarios that excluded certain costs from the public payer perspective, the ICER lowered in all instances. For instance, if community and residential care costs are not be covered by public health care systems, voretigene neparvovec would be expected to have an incremental cost of $1,023,447 and 5.62 additional QALYs when compared with BSC (ICER = $195,143 per QALY).

Overall, the scenario analyses demonstrated that the model was not sensitive to: the use of utility estimates based on the Health Utility Index (based on physician proxy), assuming no increased mortality risk due to blindness, excluding crossover trial data, and using MSM estimates fitted on non-imputed data (i.e., less than a 5% change in ICER estimates relative to the CADTH base case).

CADTH also undertook an exploratory analysis to present estimates on the effect of the possibility of re-treatment as raised by clinical experts consulted by CADTH. The exploratory re-treatment scenario assumed that 50% of patients who receive voretigene neparvovec would receive it again 10 years after initial therapy, when the treatment effect starts to wane. Re-treatment was assumed to be associated with an additional 5 years of benefit. This was modelled by assuming a 12.5-year treatment effect for the whole cohort, representing an average of 50% of patients who receive 10 years of treatment benefit plus 50% of patients who receive 15 years of treatment benefit (i.e., given the yearly cycle length, treatment effects were modelled up 13 years). Additionally, re-treatment costs for the 50% of patients were included, appropriately discounted. This exploratory analysis found that permitting re-treatment could result in an increase in the ICER of 18% based on the aforementioned assumptions.

## Table 14: Scenario Analyses Results

| Scenario | Treatment | Total costs ($) | Total QALYs | ICER ($/QALYs) |
|---|---|---|---|---|
| CADTH base case reanalysis | BSC | 308,932 | 17.60 | – |
| | VN | 1,328,815 | 22.69 | 200,477 |
| 20-year duration of treatment effect | BSC | 309,310 | 17.52 | – |
| | VN | 1,310,198 | 24.71 | 139,249 |
| 15-year duration of treatment effect | BSC | 308,557 | 17.69 | – |
| | VN | 1,318,155 | 23.88 | 163,002 |
| HUI utility estimates[6] | BSC | 308,783 | 5.89 | – |
| | VN | 1,328,982 | 10.87 | 204,948 |
| Excluding genetic testing related costs | BSC | 309,006 | 17.58 | – |
| | VN | 1,296,567 | 22.64 | 195,143 |
| Excluding vision aid costs | BSC | 280,482 | 17.57 | – |
| | VN | 1,300,903 | 22.64 | 201,092 |
| Excluding community and residential care costs | BSC | 245,097 | 19.13 | – |
| | VN | 1,268,544 | 24.75 | 182,091 |
| Excluding vision aid and community and residential care costs | BSC | 213,190 | 17.64 | – |
| | VN | 1,236,911 | 22.74 | 200,535 |
| Using a societal perspective | BSC | 1,787,184 | 17.68 | – |
| | VN | 2,577,625 | 22.75 | 155,714 |
| Assuming no mortality effect[5] | BSC | 319,944 | 17.79 | – |
| | VN | 1,339,544 | 22.88 | 200,346 |
| MSM estimates fitted on non-imputed data | BSC | 303,433 | 17.72 | – |
| | VN | 1,318,871 | 23.02 | 191,531 |
| Excluding crossover trial data | BSC | 309,582 | 17.51 | – |

| Scenario | Treatment | Total costs ($) | Total QALYs | ICER ($/QALYs) |
|---|---|---|---|---|
| | VN | 1,322,786 | 22.75 | 193,446 |
| Removing the 25% relative risk reduction in vision deterioration after VN treatment effect has ended | BSC | 308,832 | 17.54 | – |
| | VN | 1,333,750 | 22.14 | 222,899 |
| Re-treatment modelled (exploratory analysis) | BSC | 308,550 | 17.63 | – |
| | VN | 1,460,942 | 23.79 | 237,165 |

BSC = best supportive care; HUI = Health Utility Index; ICER = incremental cost-effectiveness ratio; MSM = multistate model; QALY = quality-adjusted life-year; VN = voretigene neparvovec.

## Table 15: Disaggregated Summary of CADTH's Economic Evaluation Results (Societal Perspective)

| Parameter | New treatment | Comparator | Incremental | Percentage (of total incremental)[a] |
|---|---|---|---|---|
| | **Discounted QALYs** | | | |
| **Total** | **22.75** | **17.68** | **5.08** | **100%** |
| Health state 1 | 10.21 | 3.13 | 7.08 | 139% |
| Health state 2 | 5.52 | 3.05 | 2.48 | 49% |
| Health state 3 | 2.78 | 4.91 | −2.13 | −42% |
| Health state 4 | 1.51 | 2.18 | −0.67 | −13% |
| Health state 5 | 2.74 | 4.41 | −1.67 | −33% |
| Adverse event disutility | −0.01 | 0.00 | −0.01 | 0% |
| Caregiver disutility | 0.00 | 0.00 | 0.00 | 0% |
| | **Discounted costs ($)** | | | |
| **Total** | **2,577,625** | **1,787,184** | **790,441** | **100%** |
| Voretigene neparvovec | 1,035,078 | – | 1,035,078 | 131% |
| Eligibility testing | 32,760 | – | 32,760 | 4% |
| Adverse events | 769 | – | 769 | 0% |
| Health care resource use | 259,620 | 308,379 | −48,759 | −6% |
| Hospitalization | 39,322 | 49,775 | −10,453 | −1% |
| General ophthalmic services | 129,013 | 163,327 | −34,314 | −4% |
| Vision assistance and aids | 28,596 | 28,456 | 140 | 0% |
| Residential car | 58,682 | 62,549 | −3,867 | 0% |
| Community care | 4,007 | 4,272 | −265 | 0% |
| Non–health care resource use | 1,249,399 | 1,478,805 | −229,406 | −29% |
| Home modifications | 58,580 | 63,855 | −5,275 | −1% |
| Disability pension | 64,158 | 87,617 | −23,459 | −3% |
| Caregiver productivity loss | 585,227 | 584,588 | 639 | 0% |
| Education | 6,215 | 11,488 | −5,273 | −1% |
| Productivity loss | 535,218 | 731,258 | −196,040 | −25% |
| ICER ($/QALY) | 155,714 | | | |

BSC = best supportive care; HS = health state; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

# Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

**Key takeaways of the budget impact analysis**

- CADTH identified the following key limitations with the sponsor's analysis:
  - the number of patients eligible for voretigene neparvovec is highly uncertain
  - the proportion of prevalent cases that will receive a diagnosis and be treated in the first 3 years of the analysis is uncertain
  - some drug costs were not included in the public payer perspective
  - genetic testing costs were not applied to incident cases
  - some inputs were not aligned with those used in the submitted pharmacoeconomic analysis.
- The CADTH reanalyses included aligning the percentage of patients diagnosed in Ontario with other jurisdictions, capturing all drug costs from the public payer perspective, adding genetic testing costs for incident RP and LCA cases, and aligning the approach to model retinal cell viability testing costs with that taken in the pharmacoeconomic analysis.
- Based on the CADTH reanalyses, the budget impact from the introduction of voretigene neparvovec is expected to be $28,882,120 in year 1, $24,756,103 in year 2 and $17,535,573 in year 3 with a 3-year total budget impact of $71,173,796 from the public payer perspective. From a health care system perspective, the 3-year total budget impact was estimated to be $77,885,351. Significant uncertainty remains regarding the proportion of pre-existing patients who will be identified during the 3-year time horizon, as well as with the epidemiological inputs used to derive the number of eligible patients, both of which have considerable influence on the results. Given uncertainty regarding the number of patients with *RPE65*-mediated IRD, CADTH noted that the 3-year budget impact could be as high as $116,559,985 from a public payer perspective.

## Summary of Sponsor's Budget Impact Analysis

In the submitted budget impact analysis (BIA), the sponsor assessed the expected budgetary impact resulting from reimbursing voretigene neparvovec for the treatment of adult and pediatric patients with vision loss due to IRD caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells.[1] The base-case analysis was conducted from the perspective of Canadian public drug plans over a 3-year time horizon.

The sponsor estimated the current population size using an epidemiological-based approach, using prevalence to estimate the total number of pre-existing cases and incidence to estimate the number of new cases (Table 16). The sponsor assumed that only a proportion of prevalent cases would be diagnosed over the 3 years, while all incident cases would be diagnosed (Table 16). While 60% of prevalent cases were assumed to have sufficient viable retinal cells and were therefore eligible for voretigene neparvovec, it was assumed that all incident cases identified with *RPE65* mutation would be eligible to receive voretigene neparvovec. In the world with voretigene neparvovec, it was assumed all patients eligible for voretigene neparvovec would be treated.

The sponsor's base case was based on a public payer perspective that considered only the costs of voretigene neparvovec. Scenario analyses were conducted that adopted a broader drug plan perspective that further included the costs of genetic testing, and a health care system perspective that included the aforementioned costs as well as administration costs (i.e., immunomodulatory regimen and surgery), and the costs to determine eligibility for voretigene neparvovec (i.e., OCT test). Genetic testing costs were applied only to prevalent cases of RP and LCA who received testing for *RPE65* mutation with an additional assumption that 10% of prevalent patients would have been previously tested at baseline. It

was assumed that no cost would be associated with the reference scenario (i.e., without reimbursement of voretigene neparvovec).

## Table 16: Summary of Key Model Parameters

| Parameter | Sponsor's estimate (reported as year 1 / year 2 / year 3, if appropriate) |
|---|---|
| **Target population** | |
| Prevalence of RP | 0.025%[15] |
| Proportion of RP due to *RPE65* mutation | 1.404%[16,17] |
| Incidence of RP | 0.0006%[18] |
| Prevalence of LCA | 0.003%[19] |
| Proportion of LCA due to *RPE65* mutation | 6.80%[20] |
| Incidence of LCA | 0.000072%[a] |
| Proportion of prevalent cases who are diagnosed with *RPE65*-mediated IRD | 25% / 20% / 15%[b] |
| Proportion of diagnosed patients with sufficient viable retinal cells | 60%[c] |
| Number of patients eligible for the drug under review | 43 / 25 / 18 |
| **Market uptake (3 years)** | |
| Uptake (reference scenario) | |
| VN | 0% / 0% / 0% |
| Uptake (new drug scenario) | |
| VN | 100% / 100% / 100% |
| **Cost of treatment (per patient)** | |
| Cost of drug | |
| Voretigene neparvovec | $1,031,500[d] |
| Health care system costs | |
| Genetic testing | $1,333.33[21] |
| Testing for sufficient viable retinal cells | $128[22] |
| Immunomodulatory regimen | $4.29[23] |
| Surgery for drug administration | $3,063.48[24] |

IRD = inherited retinal dystrophy; LCA = Leber congenital amaurosis; RP = retinitis pigmentosa; RPE65 = retinal pigment epithelium 65 kDa protein.

[a] Assumption (based on the ratio of prevalence for RP:LCA and the incidence for RP).

[b] Assumption. In Ontario, the proportion of pre-existing cases who are currently diagnosed with *RPE65*-mediated IRD differed (i.e., year 1: 50%, year 2: 20%, year 3: 15%).

[c] Assumption. In Study 301, examiners estimated that sufficient viable retinal cells would be found in 50% to 60% of diagnosed patients.[1]

[d] Sponsor's submitted price.

## Summary of the Sponsor's BIA Results

The budget impact from the drug plan perspective of reimbursing voretigene neparvovec for patients with *RPE65*-mediated IRD is expected to be $44,354,500 in year 1, $25,787,500 in year 2, and $18,567,000 in year 3, with a total 3-year budget impact of $88,709,000. Among alternative perspectives considered by the sponsor, the 3-year budget impact was $95,698,852 and $98,973,689 from a broader drug plan perspective and from a health care system perspective, respectively.

## CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Uncertainty regarding the number of patients eligible to receive voretigene neparvovec**. As noted by the sponsor in its submission, uncertainty remains regarding the prevalence and incidence of RP and LCA, and the proportion of these cases mediated by *RPE65*.[1] Additionally, according to clinical experts consulted by CADTH, classifying disease based on clinical manifestations, such as RP and LCA, is no longer common practice, adding uncertainty regarding the values used to estimate the number of patients with RPE-mediated IRD. Treatment with voretigene neparvovec further requires patients to have sufficient viable retinal cells. Although the sponsor assumed 60% of existing cases would have sufficient viable retinal cells, the clinical experts consulted by CADTH and CADTH's Clinical Review Report both noted challenges in establishing a definition for this criterion. Clinical experts have noted that there is no benchmark or threshold to define viable retinal cells. Additionally, clinical experts indicated that measuring viable retinal cells is not straightforward, as supported by the sponsor's implementation plan, which noted that OCT exams are more qualitative and supplemented by additional tests for visual acuity and function.[3] Given the uncertainty of this definition, the proportion of *RPE65*-mediated IRD cases expected to have viable cells remains uncertain.
    - CADTH explored alternative epidemiological estimates to derive the eligible patient population in scenario analyses using pessimistic and optimistic estimates. CADTH further conducted sensitivity analyses testing a range (50% and 80%) for the proportion of patients with viable retinal cells.
- **Uncertainty regarding the identification of pre-existing cases.** In the sponsor's base case, it was assumed that a proportion of prevalent cases would be diagnosed prior to the introduction of voretigene neparvovec, and that a proportion of prevalent cases would remain undiagnosed (40% for all jurisdictions apart from Ontario, 15% in Ontario) 3 years following its introduction. According to clinical experts consulted by CADTH, these estimates (i.e., the proportion of patients currently diagnosed and the proportion of patients who remain undiagnosed) are uncertain. The identification of existing cases depends on a number of factors, including the availability of genetic testing which, according to feedback from public drug plans, may not be available locally, may require sending samples out-of-province or out-of-country for analysis, and may not be funded through provincial, ministerial, or local laboratory budgets. Further, the clinical experts consulted by CADTH did not expect a difference in the percentage of patients diagnosed in Ontario compared with other jurisdictions.
    - In the CADTH base case reanalyses, the percentage of patients diagnosed in Ontario was aligned with the other jurisdictions. As there is no evidence regarding the proportion of prevalent *RPE65*-mediated IRD patients who would be diagnosed at baseline, or the proportions of prevalent patients who would be diagnosed within the 3 years following the introduction of voretigene neparvovec, CADTH conducted a scenario analysis that assumed all prevalent *RPE65*-mediated IRD patients would be diagnosed and, if their retinal cells were viable, would be treated.
- **Immunomodulatory regimen drug costs were not captured in the public payer's perspective.** Although the sponsor's health care system perspective included the costs of an immunomodulatory drug regimen, these drug costs were inappropriately excluded from the public payer perspective.
    - In the CADTH base case reanalyses, the cost of prednisone (taken during administration of voretigene neparvovec) was incorporated into the public payer perspective.

- **Costs of genetic testing were considered only for prevalent patients.** In the sponsor's health care system perspective, the costs of genetic testing were considered in prevalent IRD patients, and the cost of testing incident RP and LCA cases for *RPE65* was not included.
  - In the CADTH base case reanalyses, the cost of testing incident cases in years 1, 2, and 3 was incorporated.
- **Approach to model cell viability was not aligned with the pharmacoeconomic analysis.** OCT costs were considered only for patients who receive voretigene neparvovec treatment, whereas the pharmacoeconomic analysis adopted a broader consideration, including the costs associated with testing IRD patients who may not have sufficient viable retinal cells. Furthermore, 55% of prevalent patients tested for cell viability would have sufficient viable cells in the economic evaluation as opposed to the 60% that was assumed in the BIA.[1]
  - In the CADTH base case reanalyses, the approach to account for the cost of OCT testing was aligned with the approach used in the pharmacoeconomic analysis.

## CADTH Reanalyses of the BIA

A summary of the changes made to the sponsor's BIA as part of the CADTH reanalysis is available in Table 17.

### Table 17: CADTH Revisions to the Submitted BIA

| Stepped analysis | Sponsor's value or assumption | CADTH value or assumption |
|---|---|---|
| **Corrections to sponsor's base case** | | |
| None | | |
| **Changes to derive the CADTH base case** | | |
| 1. Proportion of prevalent cases in Ontario diagnosed at baseline | 50% | 25% |
| 2. Immunomodulatory regimen costs | Included in the health care system perspective only | Included in the public payer perspective |
| 3. Genetic testing costs | Applied to prevalent RP and LCA cases | Applied to prevalent and incident RP and LCA cases |
| 4a. Proportion of patients with sufficient viable retinal cells | 60% | 55% |
| 4b. Retinal cell viability testing costs | Applied only to patients who receive voretigene neparvovec (i.e., patients with *RPE65*-mediated IRD with sufficient viable cells) | Applied to all patients diagnosed with *RPE65*-mediated IRD |
| CADTH base case | | 1 + 2 + 3 + 4a + 4b |

LCA = Leber congenital amaurosis; RP = retinitis pigmentosa; RPE65 = retinal pigment epithelium 65 kDa protein.

Applying these changes resulted in a decrease in the budget impact from both the public payer and health care system perspective. From the public payer perspective, 3-year total costs were estimated to be $71,173,796. The results of the CADTH stepwise reanalysis are presented in summary format in Table 18 and a more detailed breakdown is presented in Table 19.

## Table 18: Summary of the CADTH Reanalyses of the BIA

| Stepped analysis | 3-year total | |
|---|---|---|
| | Public payer perspective ($) | Health care system perspective ($) |
| Submitted base case | 88,709,000 | 95,973,689 |
| CADTH reanalysis 1 | 76,331,000 | 82,187,402 |
| CADTH reanalysis 2 | 88,709,369 | 95,973,689 |
| CADTH reanalysis 3 | 88,709,000 | 96,304,626 |
| CADTH reanalysis 4a | 82,520,000 | 89,765,514 |
| CADTH reanalysis 4b | 88,709,000 | 96,026,727 |
| CADTH base case | 71,173,796 | 77,885,351 |

CADTH also conducted additional scenario analyses to address the remaining uncertainty regarding the potential size of the eligible population:

Analysis 1 Assumed that 100% of prevalent patients would be identified and treated over the 3-year time horizon.

Analysis 2 Used the lower estimate in the size of the patient population with *RPE65*-mediated IRD: the lower estimate from Wang et al. (0.81%) for the percentage of RP that is *RPE65*-mediated[16] and the lower LCA prevalence estimate from Fighting Blindness Canada (1 in 50,000, 0.002%).[19]

Analysis 3 Used the upper estimate in the size of the patient population with *RPE65*-mediated IRD: the higher RP prevalence estimate from Fighting Blindness Canada (1 in 3,500, 0.029%)[15] and higher estimates from Morimura et al. for the percentage of RP and LCA that is *RPE65*-mediated (1.85% and 15.56%, respectively).[17]

Analysis 4 Assumed 40% of patients with pre-existing diagnosis with *RPE65*-mediated IRD will have viable retinal cells.

Analysis 5 Assumed 80% of patients with pre-existing diagnosis with *RPE65*-mediated IRD will have viable retinal cells.

Analysis 6 Used a reduced price for voretigene neparvovec (based on the CADTH price-reduction analysis) in which voretigene neparvovec would be cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained ($257,875).

Given the high costs associated with voretigene neparvovec, uncertainties in the number of eligible patients have significant potential to influence the BIA results (Table 20). Assuming all prevalent patients would be identified over the 3-year time horizon increased the budget impact in the public payer perspective to $109,339,455 (Table 20). The high and low estimates for the number of patients with *RPE65*-mediated IRD had the largest influence on results, with an estimated total budget impact of $49,512,206 and $116,559,985, respectively.

## Table 19: Detailed Breakdown of the CADTH Reanalyses of the BIA

| Stepped analysis | Scenario | Year 1 ($) | Year 2 ($) | Year 3 ($) | 3-year total ($) |
|---|---|---|---|---|---|
| Submitted base case | Reference | 0 | 0 | 0 | 0 |
| | New drug | 44,354,500 | 25,787,500 | 18,567,000 | 88,709,000 |
| | Budget impact | 44,354,500 | 25,787,500 | 18,567,000 | 88,709,000 |
| CADTH base case | Reference | 0 | 0 | 0 | 0 |
| | New drug | 28,882,120 | 24,756,103 | 17,535,573 | 71,173,796 |
| | Budget impact | 28,882,120 | 24,756,103 | 17,535,573 | 71,173,796 |
| CADTH scenario analysis: drug plan perspective (plus diagnostic testing) | Budget impact | 30,841,172 | 27,280,361 | 19,501,051 | 77,622,585 |
| CADTH scenario analysis: health care system perspective | Budget impact | 30,947,802 | 27,371,758 | 19,565,791 | 77,885,351 |

## Table 20: CADTH Scenario Analyses

| Scenario | Budget impact, by perspective | Year 1 ($) | Year 2 ($) | Year 3 ($) | 3-year total ($) |
|---|---|---|---|---|---|
| CADTH base case | Public payer | 28,882,120 | 24,756,103 | 17,535,573 | 71,173,796 |
| | Health care system | 30,947,802 | 27,371,758 | 19,565,791 | 77,885,351 |
| Assume 100% of pre-existing patients are identified | Public payer | 28,882,120 | 23,724,599 | 56,732,736 | 109,339,455 |
| | Health care system | 30,947,802 | 26,336,445 | 63,403,598 | 120,687,846 |
| Lower patient number estimate (size of prevalent population = 129) | Public payer | 21,661,590 | 17,535,573 | 10,315,043 | 49,512,206 |
| | Health care system | 23,630,649 | 20,034,418 | 12,248,408 | 55,913,475 |
| Higher patient number estimate (size of prevalent population = 378) | Public payer | 49,512,206 | 39,197,163 | 27,850,616 | 116,559,985 |
| | Health care system | 51,585,443 | 42,149,163 | 30,130,220 | 124,144,826 |
| Assume 40% of patients have sufficient viable retinal cells | Public payer | 24,756,103 | 19,598,582 | 11,346,547 | 55,701,232 |
| | Health care system | 26,808,647 | 22,196,853 | 13,354,876 | 62,360,376 |
| Assume 80% of patients have sufficient viable retinal cells | Public payer | 40,228,667 | 33,008,137 | 24,756,103 | 97,992,908 |
| | Health care system | 42,333,403 | 35,651,930 | 26,811,233 | 104,796,567 |
| Price of voretigene neparvovec reduced to $257,875 | Public payer | 7,220,620 | 6,189,103 | 4,383,948 | 17,793,671 |
| | Health care system | 9,286,302 | 8,804,758 | 6,414,166 | 24,505,226 |

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